

# THE EXPERIMENTAL CONTROL OF PROLONGED PREGNANCY IN THE LACTATING RAT BY MEANS OF ESTROGEN <sup>1</sup>

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TWO PLATES (SIXTEEN FIGURES)

Since Lataste (1887, 1891) first described prolonged gestation in lactating rodents, numerous investigators have attempted to explain this curious phenomenon. According to some, the length of the lactating pregnancy is correlated with the number of suckling young (Daniel, '10; King, '13; Enzmann, Saphir and Pincus, '32; Weichert, '40). Others report that it bears no definite relationship to the number of young suckling or to the number developing in the uterus (Kirkham, '16 a, b, '18; Mirskaia and Crew, '30; Hain, '34; Krehbiel, '41 a). Additional data obtained by the author (unpublished) reaffirm the former contention.

Early workers on the problem attributed prolonged gestation to inanition, but Kirkham ('16 a, b, '18), working with mice, found it to be due to delayed implantation. When the blastocysts enter the uterus they do not implant immediately and development comes to a halt. The blastocysts lie free in the lumen of the uterus for a number of days before implantation occurs.

It has recently been shown that altered endocrine factors are responsible for prolonged gestation. Weichert ('40) demonstrated that injections of Antuitrin-S into inseminated

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rats suckling large litters brings about implantation, development and even delivery at a time comparable to that of a normal pregnant rat. The heavily luteinized ovaries of the injected rats, despite their atypical appearance, suggested that delayed implantation was due to insufficiency of progesterone. However, injections of progesterone in inseminated lactating rats failed to bring about early implantation.

The successful use of Antuitrin-S in reducing the time of prolonged gestation to normal, does not explain a great deal since this substance is not known to be a definite chemical entity. The author has therefore undertaken a more comprehensive investigation of the problem.

Experiments of Hain ('35 a, b, '36), Greene ('37) and Weichert and Kerrigan ('41) show that estrogens injected into lactating female rats will pass through the mammary glands in appreciable quantities and have a profound effect upon the urogenital systems of the suckling young. It occurred to the writer that perhaps under normal conditions, the suckling young were depleting the maternal organism of estrogens directly or indirectly necessary for proper sensitization of the uterus. Replacing estrogens in the mother or bringing them up to the normal level should then satisfy the conditions for normal implantation. The observations presented here are in accord with this idea. According to the above interpretation, the follicle-stimulating effect of Antuitrin-S would account for the positive results mentioned above.

Krehbiel ('41 a) in the meantime, by a different line of reasoning, had come to much the same conclusion. He suggests that the uterus of a lactating rat is sensitized only at certain time intervals and only during these times may implantation occur. The correlation of the rhythm of these periods with that of the estrous cycle indicates that a sort of subthreshold cycle may be taking place. Krehbiel ('41 b) has recently reported that injections of theelin administered during the pre-implantation period of pregnant lactating rats leads to implantation on day 6. The embryos were resorbed. Additional injections of estrogen during the post-implantation period failed to maintain the developing embryos. In seven

cases out of thirty-six, under the influence of estrogen injections, pregnancies were brought to term on days  $22\frac{1}{2}$  or  $24\frac{1}{2}$ . These were interpreted as cases where pregnancies were not interrupted by the concurrent lactation.

The data obtained from the experiments reported here, throw a different light upon the problem. They show that injected estrogen may fully satisfy the conditions necessary for reducing the length of gestation to that of a normal pregnant rat.

#### MATERIAL AND METHODS

All rats used in these experiments were virgin females of the Sprague-Dawley strain, of known ages and weighing from 200 to 260 gm. Vaginal smears were taken routinely. The day before parturition was expected, each rat was placed with a sexually mature male in an individual cage. For the sake of uniformity the number in the litter was adjusted to nine immediately after parturition. In some this meant reducing the litter; in others it was necessary to add pups of the same age. If spermatozoa were found in the vagina within 24 to 36 hours, the rat was used in the experiment. If no spermatozoa were found she was discarded. Males were removed from the cages as soon as spermatozoa were found. Thus each mother was isolated with nine young until the experiment was terminated. Weights of all mothers and litters were recorded daily and the number in the litter checked. If any young died, they were replaced by others selected from the general colony and as nearly as possible of the same age.

Intramuscular injections of theelin in oil were given to 123 inseminated rats each suckling a litter of nine. The theelin was given in varying amounts and at different times as described below. Forty-nine similar but uninjected animals served as controls. In both series some animals were permitted to go to term. Most, however, were sacrificed at different times during gestation and their reproductive organs preserved for study. The reproductive organs of fifty-four non-lactating pregnant rats, sacrificed at different stages during pregnancy were used for comparison.

Since the date of insemination for each experimental animal was known it was possible to calculate with accuracy the number of days delay in implantation. The actual day of implantation and the time when parturition would have occurred could thus be estimated with precision.

The appearance of free blood in the vagina gave evidence of resorption of some or all of the embryos. This was always confirmed by manual palpation of the uteri.

#### OBSERVATIONS

Of the forty-nine inseminated lactating rats suckling nine young which served as controls, twelve were permitted to go to term. Fourteen were sacrificed at times when the implantation sites in their uteri were macroscopically visible (figs. 10, 13, 14, 15, 16). The probable days of parturition were then calculated. Implantation dates of all twenty-six pregnancies were estimated from the actual or calculated times of parturition (table 1). The gestation periods of these rats ranged

TABLE 1

*The day of implantation and the length of gestation in twenty-six inseminated lactating rats each suckling nine young.*

| NUMBER<br>OF<br>ANIMALS | ESTIMATED<br>DAY OF<br>IMPLANTATION | LENGTH<br>OF<br>GESTATION * |
|-------------------------|-------------------------------------|-----------------------------|
| 1                       | 11                                  | 27 a                        |
| 1                       | 11                                  | 27 e <sup>1</sup>           |
| 1                       | 13                                  | 29 e                        |
| 2                       | 14                                  | 30 a                        |
| 2                       | 14                                  | 30 e                        |
| 1                       | 15                                  | 31 e                        |
| 3                       | 16                                  | 32 a                        |
| 1                       | 16                                  | 32 e                        |
| 3                       | 17                                  | 33 a                        |
| 3                       | 18                                  | 34 a                        |
| 3                       | 18                                  | 34 e                        |
| 1                       | 19                                  | 35 e                        |
| 1                       | 21                                  | 37 e                        |
| 1                       | 22                                  | 38 e                        |
| 2                       | 24                                  | 40 e                        |

\* a — Refers to actual length of gestation.

e — Refers to calculated length of gestation.

<sup>1</sup> The mortality of the young of this animal was high.

from 27 to 40 days with an average of 32.9 days. Their dates of implantation varied accordingly from 11 to 24 days with an average of 16.9.

Of the 123 inseminated lactating rats suckling nine young and injected with theelin, sixteen or 13% failed to become pregnant since they ultimately came into estrus without having shown the placental sign or the bloody discharge indicative of resorption. Implantation occurred in all but two of the remaining 107 animals as a result of theelin injection. They either gave evidence of resorption or else normal implantation sites and embryos were observed. In four cases normal young were born on the twenty-third day.

In the preliminary work relatively large doses of theelin were administered (table 2). Out of twenty-one rats injected with doses of 25 to 100 IU at different times, resorption occurred in all but six. These, at time of sacrifice, had fetuses developed to the same degree as those of non-lactating pregnant rats on the corresponding day of pregnancy.

Since estrogens in large doses are unfavorable for normal pregnancy, it seemed that perhaps smaller doses would yield more favorable results. Accordingly, sixty-one inseminated lactating rats suckling nine pups were injected at different times with 10 IU of theelin. Since the days of administration were determined largely by trial and error, it was not to be expected that all would respond favorably. Thirty-four of these rats resorbed their young and twenty-seven gave positive results. However, if only those are considered in which injections were begun on days 3, 4 or 5 and continued daily through the eleventh to fourteenth and in three cases even more days, then of thirty-two animals, twenty-two or 68% responded by implantation and development like that of a normal, non-lactating pregnant rat (table 3 and plates 1 and 2). It made no difference whether injections were begun on days 3, 4 or 5 for the degree of development on any subsequent day was the same.

Eleven inseminated rats each suckling nine young were given injections of 10 IU theelin beginning on days 6, 8, 10,

TABLE 2

*The effects of injecting doses of 25 to 100 IU of theelin into inseminated lactating rats suckling nine young.*

| RAT  | AMOUNT | DAY |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    | RESULT |
|------|--------|-----|---|---|---|---|---|---|---|---|----|----|----|----|----|----|----|----|----|----|----|----|--------|
|      |        | 1   | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 |        |
| D759 | 25 IU  |     |   |   | x |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    | Re.    |
| D767 | 100 IU |     |   |   | x |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    | Re.    |
| D704 | 25 IU  |     |   |   |   | x |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    | Re.    |
| D763 | 25 IU  |     |   |   |   | x |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    | Re.    |
| D762 | 50 IU  |     |   |   |   | x |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    | Re.    |
| D750 | 100 IU |     |   |   |   | x |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    | Re.    |
| D774 | 25 IU  |     |   |   | x | x | x | x | x | x | x  | x  | x  | x  | x  |    |    |    | K  |    |    |    | Pos.   |
| D772 | 50 IU  |     |   |   | x | x | x | x | x | x | x  | K  |    |    |    |    |    |    |    |    |    |    | Pos.   |
| D808 | 50 IU  |     |   |   | x | x | x | x | x | x | x  | x  | x  | x  | x  | x  | x  | x  | x  | x  | x  | K  | Re.    |
| D786 | 25 IU  |     |   |   | x | x | x | x | x | x | x  | x  | x  | x  | x  | x  | x  | x  | x  | x  | x  | K  | Re.    |
| D784 | 25 IU  |     |   |   | x | x | x | x | x | x | x  | x  | x  | x  | x  |    |    |    |    |    |    | K  | Re.    |
| D801 | 25 IU  |     |   |   | x | x | x | x | x |   |    |    |    |    |    |    |    |    |    |    |    |    |        |
|      | 50 IU  |     |   |   |   |   |   |   |   |   | x  | x  | x  | x  | K  |    |    |    |    |    |    |    | Re.    |
| D807 | 25 IU  |     |   |   | x | x | x | x | x |   |    |    |    |    |    |    |    |    |    |    |    |    |        |
|      | 50 IU  |     |   |   |   |   |   |   |   |   | x  | x  | x  | x  | x  |    |    |    |    |    |    |    | Re     |
| D816 | 25 IU  |     |   | x | x | x | x | x | x |   |    |    |    |    |    |    |    |    |    |    |    |    |        |
|      | 50 IU  |     |   |   |   |   |   |   |   |   | x  | x  | x  | x  | x  |    |    |    |    |    |    | K  | Re.    |
| D834 | 25 IU  |     |   |   | x | x | x | x | x |   |    |    |    |    |    |    |    |    |    |    |    |    |        |
|      | 50 IU  |     |   |   |   |   |   |   |   |   | x  | x  | x  | x  | x  |    |    |    |    |    |    | K  | Pos.   |
| D837 | 25 IU  |     |   | x | x | x | x | x | x |   |    |    |    |    |    |    |    |    |    |    |    |    |        |
|      | 50 IU  |     |   |   |   |   |   |   |   |   | x  | x  | x  | x  | x  |    |    |    |    |    |    | K  | Pos.   |
| D782 | 25 IU  |     | x | x | x | x |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |        |
|      | 50 IU  |     |   |   |   | x | x | x | x |   |    |    |    |    |    |    |    |    |    |    |    |    |        |
|      | 75 IU  |     |   |   |   |   |   |   |   |   |    | x  | x  | x  | x  |    |    |    |    |    |    | K  | Re.    |
| D793 | 25 IU  |     | x | x | x | x |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |        |
|      | 50 IU  |     |   |   |   | x | x | x | x | x |    |    |    |    |    |    |    |    |    |    |    |    |        |
|      | 75 IU  |     |   |   |   |   |   |   |   |   |    | x  | x  | x  | x  |    |    |    |    |    |    | K  | Re.    |
| D776 | 25 IU  |     |   |   | x | x | x | x |   |   |    |    |    |    |    |    |    |    |    |    |    |    |        |
|      | 50 IU  |     |   |   |   |   |   |   |   | x | x  | x  | K  |    |    |    |    |    |    |    |    |    | Pos.   |
| D783 | 25 IU  |     |   |   | x | x | x |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |        |
|      | 50 IU  |     |   |   |   |   |   |   |   | x | x  | x  |    |    |    |    |    |    |    |    |    |    |        |
|      | 75 IU  |     |   |   |   |   |   |   |   |   |    | x  | x  | x  | x  |    |    |    |    |    |    | K  | Re.    |
| D799 | 25 IU  |     | x | x | x | x |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |        |
|      | 50 IU  |     |   |   |   |   |   |   |   | x | x  | x  |    |    |    |    |    |    |    |    |    |    |        |
|      | 75 IU  |     |   |   |   |   |   |   |   |   |    |    | x  | x  | x  | x  |    |    |    |    |    | K  | Pos.   |

x — Day of injection.

K — Day animal was killed.

Re. — Embryos resorbed.

Pos. — Positive result with fetuses at a state of development comparable to that of a normal non-lactating pregnant rat on the same day of pregnancy.

TABLE 3

*The effects of injecting doses of 10 IU theelin into inseminated lactating rats suckling nine young.*

| RAT  | DAY |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    | RESULT |
|------|-----|---|---|---|---|---|---|---|---|----|----|----|----|----|----|----|----|----|----|----|----|----|----|--------|
|      | 1   | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 |        |
| D795 | x   | x | x | x | x | x | x | x | x | x  | x  | x  | x  | x  |    |    |    |    |    |    | K  |    |    | Re.    |
| D859 | x   | x | x | x | x | x | x | x | x | x  | x  | x  | x  | x  |    |    |    |    |    |    | K  |    |    | Pos.   |
| D915 | x   | x | x | x | x | x | x | x | x | x  | x  | x  | x  | x  |    |    |    |    |    |    | K  |    |    | Pos.   |
| E131 | x   | x | x | x | x | x | x | x | x | x  | x  |    |    |    |    |    |    |    |    |    |    |    |    | Re.    |
| E136 | x   | x | x | x | x | x | x | x | x | x  | x  |    |    |    |    |    |    |    |    |    |    |    |    | Re.    |
| E151 | x   | x | x | x | x | x | x | x | x | x  | x  |    |    |    |    |    |    |    |    |    |    |    |    | Re.    |
| E134 | x   | x | x | x | x | x | x | x | x | x  | x  |    |    |    |    |    |    |    |    |    |    | K  |    | Pos.   |
| E150 | x   | x | x | x | x | x | x | x | x | x  | x  |    |    |    |    |    |    |    |    |    |    | B  |    | Pos.   |
| D924 | x   | x | x | x | x | x | x | x | x | x  | x  |    |    |    |    |    |    |    |    |    | K  |    |    | Pos.   |
| D933 | x   | x | x | x | x | x | x | x | x | x  | x  |    |    |    |    |    |    |    |    |    | K  |    |    | Pos.   |
| D866 | x   | x | x | x | x | x | x | x | x | x  | x  |    |    |    |    |    |    |    |    |    | K  |    |    | Pos.   |
| D895 | x   | x | x | x | x | x | x | x | x | x  | x  |    |    |    |    |    | K  |    |    |    |    |    |    | Pos.   |
| D969 | x   | x | x | x | x | x | x | x | x | x  | x  |    |    |    | K  |    |    |    |    |    |    |    |    | Re.    |
| D919 | x   | x | x | x | x | x | x | x | x | x  | x  |    |    |    | K  |    |    |    |    |    |    |    |    | Pos.   |
| D990 | x   | x | x | x | x | x | x | x | x | x  | x  |    |    |    | K  |    |    |    |    |    |    |    |    | Pos.   |
| E 60 | x   | x | x | x | x | x | x | x | x | x  | x  |    | K  |    |    |    |    |    |    |    |    |    |    | Pos.   |
| D960 | x   | x | x | x | x | x | x | x | x | x  | K  |    |    |    |    |    |    |    |    |    |    |    |    | Pos.   |
| D843 | x   | x | x | x | x | x | x | x | x | x  | x  | x  | x  | x  | x  | x  | x  | x  | x  | x  | K  |    |    | Re.    |
| D846 | x   | x | x | x | x | x | x | x | x | x  | x  |    |    |    |    |    |    |    |    |    |    |    |    | Re.    |
| D855 | x   | x | x | x | x | x | x | x | x | x  | x  |    |    |    |    |    |    |    |    |    |    |    |    | Re.    |
| D792 | x   | x | x | x | x | x | x | x | x | x  | x  |    |    |    |    |    |    |    |    |    | K  |    |    | Pos.   |
| D828 | x   | x | x | x | x | x | x | x | x | x  | x  |    |    |    |    |    |    |    |    |    | K  |    |    | Pos.   |
| D923 | x   | x | x | x | x | x | x | x | x | x  | x  |    |    |    |    |    |    |    |    |    | K  |    |    | Pos.   |
| D932 | x   | x | x | x | x | x | x | x | x | x  | x  |    |    |    |    |    |    |    |    |    |    |    |    | Re.    |
| D872 | x   | x | x | x | x | x | x | x | x | x  | x  |    |    |    |    |    |    |    |    |    |    | B  |    | Pos.   |
| D971 | x   | x | x | x | x | x | x | x | x | x  | x  |    |    |    |    |    |    |    |    |    |    | B  |    | Pos.   |
| D921 | x   | x | x | x | x | x | x | x | x | x  | x  |    |    |    |    |    |    |    |    |    | K  |    |    | Pos.   |
| D787 | x   | x | x | x | x | x | x | x | x | x  | x  | x  | x  | x  | x  | x  | x  | x  | x  | x  | x  | x  | K  | Pos.   |
| D826 | x   | x | x | x | x | x | x | x | x | x  | x  | x  | x  | x  | x  | x  | x  | x  | x  | x  | K  |    |    | Pos.   |
| D852 | x   | x | x | x | x | x | x | x | x | x  | x  |    |    |    |    |    |    |    |    |    | K  |    |    | Re.    |
| D841 | x   | x | x | x | x | x | x | x | x | x  | x  |    |    |    |    |    |    |    |    |    | K  |    |    | Pos.   |
| D842 | x   | x | x | x | x | x | x | x | x | x  | x  |    |    |    |    |    |    |    |    |    | K  |    |    | Pos.   |

x — Day of injection.

K — Day animal was killed.

B — Day on which young were born.

Re. — Embryos resorbed.

Pos. — Positive result with fetuses at a state of development comparable to that of a non-lactating pregnant rat on the same day of pregnancy.

12 or 14 (table 4). Nine of these were positive and two had pyometrous uteri at autopsy. In these rats the embryos were smaller, on the corresponding day of pregnancy, than those of animals injected earlier. On the day of autopsy, the sizes

TABLE 4  
*The effects of injecting doses of 10 IU of theelin into inseminated rats suckling nine young.*

| RAT  | DAY |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    | RESULT                                     |
|------|-----|---|---|---|---|---|---|---|---|----|----|----|----|----|----|----|----|----|----|----|----|--------------------------------------------|
|      | 1   | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 |                                            |
| D857 |     |   |   |   |   | x | x | x | x | x  | x  | x  | x  | x  |    |    |    |    |    |    |    | K Pos. — fetuses equal to 18-19 day normal |
| D927 |     |   |   |   |   | x |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    | K Pos. — fetuses equal to 18-19 day normal |
| D984 |     |   |   |   |   | x |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    | K Pos. — fetuses equal to 18-19 day normal |
| D887 |     |   |   |   |   | x |   |   |   |    |    |    |    |    |    |    |    |    | K  |    |    | Pos. — fetuses equal to 15-16 day normal   |
| D878 |     |   |   |   |   |   | x | x | x | x  | x  | x  | x  | x  | x  | x  | x  | x  | K  |    |    | Pos. — fetuses equal to 13-14 day normal   |
| D920 |     |   |   |   |   |   | x | x | x | x  | x  | x  | x  | x  | x  | x  | x  |    |    |    |    | K Pyometrous                               |
| D978 |     |   |   |   |   |   | x | x | x | x  | x  | x  | x  | x  | x  | x  | x  |    |    |    |    | K Pyometrous                               |
| E 29 |     |   |   |   |   |   | x | x | x | x  | x  | x  | x  | x  | x  | x  | x  |    |    |    |    | K Pos. — fetuses equal to 17-18 day normal |
| D884 |     |   |   |   |   |   |   |   |   | x  | x  | x  | x  | x  | x  | x  | x  | x  | x  | x  | K  | Pos. — fetuses equal to 15-16 day normal   |
| D934 |     |   |   |   |   |   |   |   |   |    |    | x  | x  | x  | x  | x  | x  | x  | x  | x  | K  | Pos. — fetuses equal to 16-17 day normal   |
| D925 |     |   |   |   |   |   |   |   |   |    |    |    |    | x  | x  | x  | x  | x  | x  | x  | K  | Pos. — fetuses equal to 13-14 day normal   |

x — Day of injection. K — Day animal was killed. Pos. — Positive result.

of the implantation sites and embryos were in inverse proportion to the length of time after insemination that injections were begun. A single injection of 10 IU on day 6, was in three cases sufficient to bring about implantation and subsequent development.

Attempts were next made to establish the minimum dose of estrogen required to bring about implantation on the sixth day after insemination. It is on this day, according to Huber ('15), that localized swellings of the uterus first indicate the position of the implanting blastodermic vesicles in the normal pregnant rat. Five inseminated rats suckling nine young were injected daily with 5 IU theelin from days 3 to 12. One resorbed and three delivered normal litters on day 24. The remaining rat, sacrificed on day 21, had fully developed living fetuses in the uterus. Three animals injected from days 3 to 12 with  $2\frac{1}{2}$  IU and three injected with  $1\frac{1}{4}$  IU resorbed their young. Three additional rats were injected daily with  $\frac{1}{2}$  IU theelin from days 3 to 9 and sacrificed on day 10. Two showed no indications of pregnancy and one had small implantation sites comparable to those of a normal rat on the seventh day of gestation. It would seem that the minimum daily dose of estrogen necessary to bring about implantation on the sixth day after insemination in rats suckling nine young, is between  $\frac{1}{2}$  and 1 IU. Daily injections of 5 to 10 IU are probably necessary to carry development further.

According to the findings reported here, once the fertilized eggs have reached the uterus and a certain amount of estrogen is present, implantation will occur. It is thus possible, by injecting estrogen, to bring about implantation in inseminated lactating rats suckling nine young at any time between days 6 and 14 to 16. After this time, implantation might occur without any superimposed influence.

#### DISCUSSION

The studies of Daniel ('10) and Enzmann, Saphir and Pincus ('32) on mice and those of King ('13) and Weichert ('40) on rats, indicate that prolongation of gestation in pregnant lactating rodents is directly correlated with the number of young suckling. The study reported by Weichert ('40) was based on observations of gestation periods of fifty-six pregnant lactating animals. Since then, a more extensive study of 140 additional uninjected animals suckling variable

numbers of young, has revealed that there is only a general correlation between the time of implantation and the number of suckling young (Weichert, unpublished data). Discrepancies from the general trend occur but are not frequent enough to make the generalization invalid.

Kirkham ('16 a, b, '18), Mirskaia and Crew ('30), Hain ('34) and Krehbiel ('41 a) are of the opinion that the number of suckling young bears but little relationship to the time of implantation. In the recent experiments of Krehbiel, there was a fairly high mortality among the suckling young. Those which died were not replaced. In the experiments reported here, the litter size was kept constant by replacement of those that had expired. This difference in procedure may account for the divergent findings of Weichert and Krehbiel, especially since the latter has shown that reduction in litter size brings about earlier implantation. Nevertheless, even when the litter size is kept constant, discrepancies occur (plate 2).

There are four variable factors which may possibly explain why implantation occurs at different times even in a group where the number of young suckled by each mother is the same. These variables are: (1) the strength of the suckling stimulus; (2) the amount of milk removed by the young; (3) the weight of the mother; (4) the amount of estrogen secreted by her ovaries. Such intangible factors as degree of maternal instinct and solicitude for the young may also play a part.

Considerable variation in the size and weight of young rats at birth has been observed. The general records of our colony show that the average birth weight of 228 litters of nine is 48.9 gm. At birth these litters ranged in weight from 37.9 gm. to 59.0 gm. It is obvious that with such extremes there might be a difference in the strength of the suckling stimulus and in the amount of milk removed from the mammary glands on any given day. This variation in litter weight may possibly be one of the causes of the discrepancies in length of gestation between rats suckling the same number of young.

Likewise, there may be considerable variation in the amount of estrogen secreted by the ovaries of different rats or by the same rat during different lactating pregnancies. The number of follicles secreting estrogen whether they rupture or become atretic, varies and is unpredictable.

It is suggested that removal of estrogen through the mothers' milk may directly or indirectly prevent the proper sensitization of the uterus necessary for implantation. The amount removed would be dependent on any or all of the factors enumerated above. It would account for such discrepancies in time of implantation as occur within any group where the number of suckling young is the same. It would also explain why implantation generally occurs later in rats suckling large litters than in those suckling small ones.

Since the amount of estrogen present in the body of a rat at any one time must be small, it is not surprising that injections of small amounts should properly sensitize the uterus. Experiments devised to test the amount of estrogen in the milk of rats are in progress but to date have not been promising. It may not be possible to detect such small quantities as would leave the body of the mother through this medium. The reports of Hain ('35 a, b, '36), Greene ('37) and Weichert and Kerrigan ('41), however, indicate that the suggestion advanced here is at least plausible. This hypothesis takes only relatively small amounts of estrogen into consideration, but to the author it seems more credible than any advanced to date. It might be well to point out, however, that in all experiments in which estrogens have been shown to pass through the mammary glands of rats, large doses were administered to the mother.

According to this theory, the reason why implantation finally occurs even when large litters are being suckled, is to be sought in the fact that when the eyes of the young open on the fifteenth day (the average for our colony) they soon seek food in the cage. The demand for milk is therefore diminished although the young may continue to suckle for 35 or even more days.

From the data presented in table 1, the different time intervals at which implantation may occur in inseminated lactating rats as postulated by Krehbiel ('41 a), are not obvious inasmuch as implantation in uninjected rats suckling nine young was found to occur at practically every day from 11 to 24. If, on the other hand, his interpretation is correct, another period of possible implantation must be added, i.e., on days 22 to 24, since some of the rats showed definite signs of such a late implantation.

It is rather difficult to understand the interpretation which Krehbiel ('41 b) has placed on the results of his experiments in which theelin was injected into pregnant lactating rats. In none of over 150 pregnant lactating rats suckling three or more young, have we encountered normal gestation periods provided the number of young in the litter was kept constant. Yet Krehbiel ('41 b) states that seven out of thirty-six rats injected with theelin, were cases in which pregnancy was not interrupted by the concomitant lactation and came to term at the normal time irrespective of the theelin injected.

The phenomenon of tubal locking of ova in mice and rabbits injected with estrogens early in pregnancy, has been described by Burdick and his co-workers (Burdick and Pincus, '35; Whitney and Burdick, '36, and Burdick, Whitney and Pincus, '37). Small doses of estrogen cause a retention of the ova in the tubes due to closure of the tubo-uterine junction.

It does not seem that with the doses employed in the above experiments tubal locking should be a major factor in the failure of pregnancy to proceed normally. In eleven of the sixteen rats which failed to show any signs of pregnancy, injections were begun before day 4 (when fertilized eggs enter the uterus). However, many others injected during these same days showed by their subsequent history that ova had not been retained in the tubes.

#### SUMMARY

The gestation periods of pregnant lactating rats suckling nine young vary between 27 and 40 days although the majority

fall between days 32 and 35. The lengthening of gestation is due to delayed implantation.

Small doses of estrogen (theelin in oil) were injected into inseminated lactating rats suckling nine young. If injections were begun on days 3, 4 or 5 and continued through the eleventh to fourteenth and in three cases even more days, then the blastocysts implanted and developed in 68% of the animals just as in normal non-lactating pregnant rats.

It is suggested that possibly in prolonged pregnancy, estrogens directly or indirectly essential for the preparation of the endometrium are being removed through the mothers' milk. Replacing estrogens in the mother or bringing them up to the normal level should then satisfy the conditions for normal implantation. The results obtained here seem to bear out this hypothesis.

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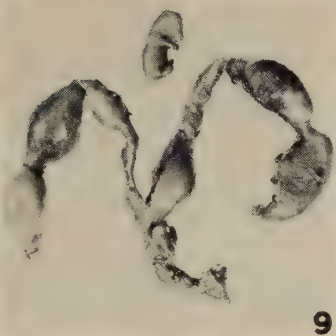
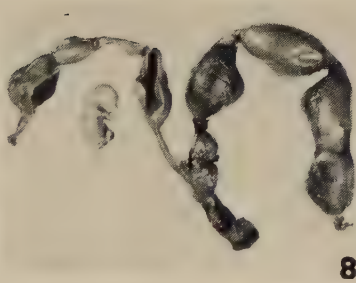
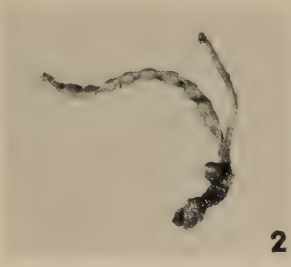
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## PLATE 1

## EXPLANATION OF FIGURES

- 1 Reproductive tract of E66, inseminated and suckling nine young; killed on tenth day of a prolonged gestation.
- 2 Reproductive tract of D360, killed on tenth day of normal pregnancy.
- 3 Reproductive tract of D957, suckling nine young and injected with 10 IU theelin from days 3 to 9. Killed on the tenth day of pregnancy.
- 4 Reproductive tract of D534, inseminated and suckling nine young; killed on fourteenth day of prolonged gestation.
- 5 Reproductive tract of D489, killed on fourteenth day of normal pregnancy.
- 6 Reproductive tract of E60, suckling nine young and injected with 10 IU theelin from days 3 to 12. Killed on fourteenth day of pregnancy.
- 7 Reproductive tract of D994, inseminated and suckling nine young; killed on eighteenth day of a prolonged gestation. Note that implantation sites are not yet visible.
- 8 Reproductive tract of D779, killed on eighteenth day of normal pregnancy.
- 9 Reproductive tract of D895, suckling nine young and injected with 10 IU theelin from days 3 to 12. Killed on the eighteenth day of pregnancy.



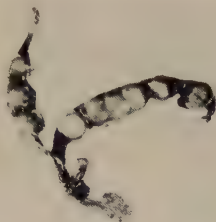
## PLATE 2

### EXPLANATION OF FIGURES

- 10 Reproductive tract of D584, suckling nine young; killed on twenty-first day of prolonged gestation.
- 11 Reproductive tract of D510, killed on twenty-first day of normal pregnancy.
- 12 Reproductive tract of D859, suckling nine young and injected with 10 IU theelin from days 3 to 14. Killed on the twenty-first day of pregnancy.
- 13 Reproductive tract of D988, suckling nine young; killed on twenty-second day of prolonged gestation.
- 14 Reproductive tract of D996, suckling nine young; killed on twenty-fourth day of prolonged gestation.
- 15 Reproductive tract of D564, suckling nine young; killed on twenty-eighth day of prolonged gestation.
- 16 Reproductive tract of D375, suckling nine young; killed on thirty-fifth day of prolonged gestation.



10



13



14



11



15



12



16



## THE EFFECTS OF POSTNATAL ANDROGENIC TREATMENT IN THE FEMALE RAT<sup>1</sup>

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TWO PLATES (SEVEN FIGURES)

In studying the effects of sex hormones on sexual differentiation in the rat, the present authors have noted that the degree of masculinization caused by androgens depends on the period of embryonic development during which the treatment is administered (Burrill and Greene, '39; Greene, Burrill and Ivy, '39). As one might expect, it was impossible to cause the development of masculine structures such as the vas deferens in the female if the anlage of this structure (wolffian duct) had already degenerated before treatment was started. Thus, after the sixteenth day of embryonic development, no amount of androgen injected into the pregnant female caused the development of a vas deferens in the female embryo.

Recently it has been reported (Selye, '40 a, b) that postnatal treatment of female rats with androgens caused "marked masculinization of the gonad and accessory sex organs . . . in some cases an epididymis and a vas deferens developed." Development of an epididymis and a vas deferens in a female rat by treatment after birth seems inconsistent with the concept that structures cannot be caused to develop when their anlagen have already degenerated.

In these same reports it was observed that the postnatal treatment of female rats with androgens caused atrophy of

<sup>1</sup>Supported by a grant from Ciba Pharmaceutical Products, Inc., Summit, New Jersey.

the uterus. In a previous study of similarly treated animals (Greene, Burril and Ivy, '38) we had casually observed, although not reported, that the uteri were relatively tremendous. In order to check on this impression and also to examine the possibility of producing an epididymis and vas deferens in the post partum female with androgens, the present study was undertaken.

#### PROCEDURE

Newborn female rats were injected subcutaneously with testosterone propionate<sup>2</sup> in sesame oil starting within 24 hours of delivery and continuing daily for 30 days. All animals received a total of 30.0 mgm. testosterone propionate during the 30 days, although two methods of treatment were used. In the first group (eight females) the dosage was kept constant, 1.0 mgm. daily. Seven of these survived the treatment period. In the second group (seventeen females) the initial dosage was smaller, but at each 5-day interval the dosage was increased to compensate for the rapidly changing weights of the animals. The total dosage, however, was also 30.0 mgm. Twelve of these animals survived.

Originally an unsuccessful attempt was made to reproduce one method of treatment used by Selye, that of intraperitoneal injection during the first 15 days. Of thirty-nine newborn females injected intraperitoneally, twenty-nine died during the first 5 days of treatment and the remainder were all dead by the twentieth day. The cause of death in all instances was probably perforation of the bowel. The abdominal cavity of the newborn and very young rat is always greatly distended, even before nursing. Structures are under tension and so crowded that it is almost impossible to insert the needle without perforating the very fragile bowel wall. Attempts to insert the needle obliquely and only a short distance into the abdominal cavity resulted in leakage of the solution or an accidental subcutaneous injection demonstrated by the appearance

<sup>2</sup> The testosterone propionate (Perandren) was furnished by Ciba Pharmaceutical Products, Inc., Summit, New Jersey.

of an oil bleb just below the skin at the injection site. However, we were able to make subcutaneous injections successfully by the following procedure: A long, fine-gauge needle was inserted under the skin of the nape and pushed well down into the lumbar region before the oil solution was ejected from the tuberculin syringe; leakage rarely occurred, even with amounts as large as 0.08 cc.

On the day after the last treatment the animals were killed and gross observations were made. The ovarian regions and portions of the uteri were removed for histological study.

#### OBSERVATIONS.

In all animals the external genitalia and vaginal orifice were modified as already reported (Greene, Burrill and Ivy, '38). The ovaries were small and in most cases hidden by the enlarged oviducts and distended ovarian capsule. The oviducts themselves had fewer convolutions than normal, but were markedly increased in diameter.

The uteri of all animals were tremendously enlarged, not only in diameter, but also in length. Instead of being straight, simple tubes as in normal untreated animals, they were coiled on themselves (one to five coils in each uterus). This coiling apparently occurred because the longitudinal growth of the uteri was greater than could be accommodated in the abdominal cavity (fig. 1).

Part of the increase in diameter of the uteri was due to distention by the contained fluid. In some cases the fluid was clear, in others it was turbid and in a few the contents were a greenish pus. There were no gross or microscopic differences between the uteri of the two treatment groups. The weights of these uteri varied from 0.3 to 2.1 gm. Remembering that these animals were only 31 days old at autopsy, these uterine weights represent a tremendous hypertrophy inasmuch as the uteri from twenty unselected adult females in our colony varied from 0.177 to 0.855 gm. As a further comparison the weights of the uteri of twenty-two normal animals of our colony only a few days younger (27 days) varied from 0.013 to 0.031 gm.

At least part of this increase in weight was undoubtedly due to the fluid present in the uteri. However, simple distention of a tubular structure by accumulated contents is generally associated with increased diameter, but not increased length. The convoluted character of these uteri indicates that a true hypertrophy has occurred.

Microscopic examination of the uterine cross sections showed villi projecting into the lumen (fig. 3). These projections were present even in the sections of distended uteri, although in such cases they were usually less prominent. The epithelium was very well developed; the cells were high columnar with many mitotic figures. The thickness of the uterine wall varied inversely with the diameter of the lumen, i.e., in the more distended uteri the wall was thinner. In all cases, however, there was good differentiation of the muscular layers. These uteri, therefore, showed no evidence of atrophy.

The entire ovarian region from eleven of these animals was serially sectioned and compared with serially sectioned ovaries from normal animals, eight of comparable age and twenty-six somewhat older or younger.

The ovaries from the treated animals were relatively minute and contained only primordial and secondary follicles (fig. 5). The ova in the latter were usually undergoing fragmentation and degeneration. The rete ovarii was more prominent than in the normal ovaries of the same age. Its ramifying tubules in certain sections occupied as much as or even more space than the ovarian cortex proper. It is doubtful, however, that the rete tubules actually were any more extensive than in the normal animals. In normals of this age and adult ovaries as well, the rete is well developed. In the treated animals, however, the marked reduction in the size of the ovary, by contrast, causes the rete to be very conspicuous.

Communicating with the rete was a group of tubules which extended a short distance from the ovary, became tortuous and formed a more or less discrete structure (fig. 7). The epithelium of these tubules was typical of efferent tubules and distinctly unlike epididymal epithelium. The presence of such efferent tubules is not surprising since similar ones are also

present in normal animals of this age. However, in the normal, the tubules are generally of smaller calibre and have a lower epithelium (fig. 6). The androgens apparently stimulated these tubules so that they became more prominent, but the androgens cannot, in any sense, be considered to have caused their presence. No epididymal structures<sup>3</sup> were found in any of the treated animals nor were there even rudimentary vasa deferentia present.

As would be expected from the gross finding of pus in the uteri, there was evidence of infection in the tissues of some of the animals. Focal, and diffuse sub-epithelial accumulations of inflammatory cells were found in the uteri, oviducts, and serosa of the ovarian capsule.

A myxomatous enlargement of the serosal portion of the oviduct wall as previously noted by Selye was present in these animals, but to a variable degree.

#### DISCUSSION

The findings in the gonads of our treated animals are essentially the same as those reported by Selye for similarly treated animals. However, the interpretations and conclusions which he derives from his observations are very different from ours. Concerning the epithelial tubules which are conspicuous in the medullary and hilar regions of these ovaries, Selye has stated “. . . transformation of the gonad may go so far that medullary tubules appear in its center” ('40 b) and “. . . it is obvious that epithelial tubules—such as are normally observed in the male gonad only—arose in the medulla of the ovary under the influence of testosterone” ('40 a). It is further implied that the tubules in question may represent male gonadal elements. In our opinion, the presence of these tubules in the ovaries of the treated animals represents merely an exaggeration of the normal condition. In normal ovaries the rete consists of well developed tubules which ramify in the medullary and hilar regions of the ovary. An occasional tubule may penetrate well into the cortical

<sup>3</sup> The epididymis and efferent tubules in the rat are embryologically and anatomically separate and discrete structures. The epididymis is derived exclusively from the wolffian duct.

region. In the experimental animals ovarian growth has been inhibited to such an extent that by contrast, the rete ovarii is much more conspicuous than it is normally. In the light of this interpretation it would be erroneous to consider that these tubules were acquired by the gonad in response to androgen therapy or that they represent, in any sense, a "masculinization of the gonad."

Selye also noted that "In several cases, a well-formed epididymis and a vas deferens were seen in the vicinity of the oviduct" ('40 a). In none of the eleven serially sectioned gonads which we examined were there epididymal tubules or vasa deferentia. Very well developed efferent tubules were found, however, and it seems possible that these tubules make up the structure which Selye regards as the epididymis. These structures, however, are normally present at birth in the female rat, are well developed in normal animals of the same age as the treated animals and persist in the adult. It is true that they are more prominent (better developed) in the androgen treated animals and form a more extensive structure than in the normals. Nevertheless, stimulation of already existing structures such as the efferent tubules is a different phenomenon from the production of an epididymis, a structure not normally present in the female even in a rudimentary state.

As already mentioned, no vas deferens or even rudiments of this structure were found in a careful search through the serial sections of the gonad regions. This negative finding, although contrary to Selye's observations, is consistent with our expectations. The part of the wolffian duct which is homologous to the vas deferens of the male has not been found in examination of eight serially sectioned normal newborn females. Embryologically, this portion of the wolffian duct completely degenerates before birth. In the absence of an appropriate anlage it is difficult to understand how androgens could produce a structure which is derived from this anlage.

In summary Selye has stated, ". . . testosterone is not merely capable of directing the development of undifferentiated embryonic genital organs into the male type, but can also

transform the fully differentiated postnatal female genitals into the male direction'' ('40 a). His evidence for this statement includes the presence of the so-called medullary tubules in the ovary and the effects on the external genitalia, i.e., suppression of the external vaginal introitus and hypertrophy of the clitoris. These latter changes he regards as similar to those produced by treatment with androgens during embryonic life. Certain important differences, however, have been overlooked. It is true that androgens administered even late in embryonic life can alter the development of the phallus so that a penis normal in all respects is produced in the female rat. This complete masculinization occurs because differentiation of the phallus is still not specific as to sex at this stage, and all the homologues requisite for perfect development of the male phallus are still present. The androgen, administered at this time, stimulates these anlagen to develop as they normally do in the male. At birth the female external genitalia are still relatively undeveloped in the female direction and treatment with androgens starting at birth can still alter the course of development in the male direction. Such alteration, however, in contrast to that consequent to prenatal stimulation, is incomplete and results in a large, but malformed penis. The effect of postnatally administered androgens is therefore not one of transforming fully differentiated structures in the male direction, but one of stimulating as yet undifferentiated male homologues.

We are unable to account for the fact that in our treated animals the uteri were stimulated, while in Selye's animals the uteri were atrophic. In his original experiment he gave his six females 1.0 mgm. testosterone propionate intraperitoneally for 15 days and then 3.0 mgm. subcutaneously for the next 15 days. This represents a higher total dose than in our experiment and a higher daily dose during the last 15 days. The higher dose of androgens, however, does not explain the difference in results since in another procedure using only 30.0 mgm., Selye obtained the same effects. In this experiment he gave 1.0 mgm. daily for 30 days (intraperitoneally the first

14 days and subcutaneously thereafter). Actually these animals received much smaller effective amounts of androgen than ours during the first 2 weeks of treatment since intraperitoneally administered testosterone propionate is relatively ineffective (Deanesly and Parkes, '37). There is a remote possibility that the lesser effective amount of androgen in the first period of treatment may explain the different effects on the uteri. This does not seem probable, but is the only definitely different aspect of the procedure which would serve as an explanation without recourse to the vague and convenient term "colony differences."

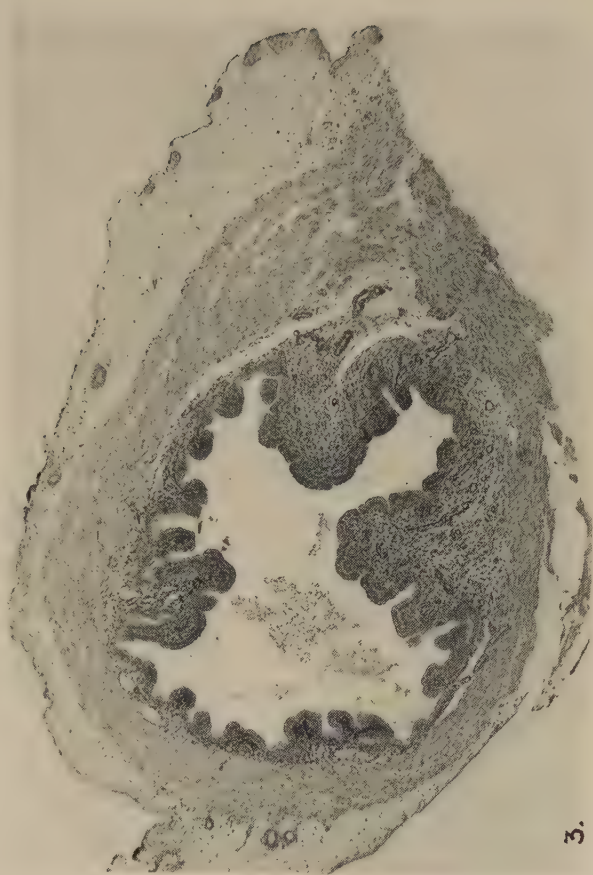
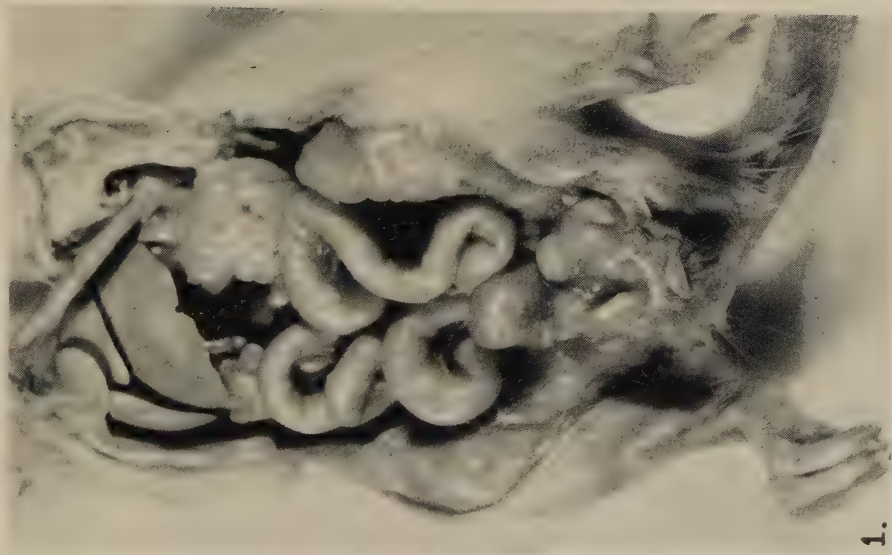
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## PLATE 1

## EXPLANATION OF FIGURES

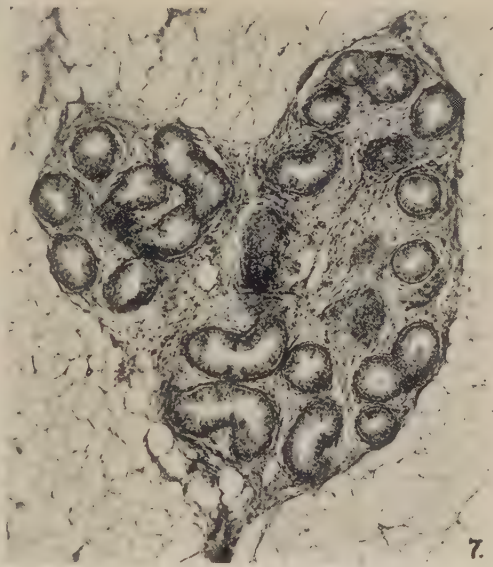
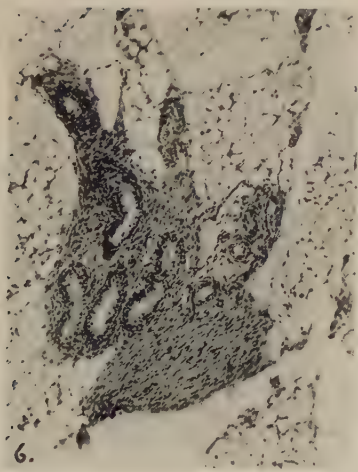
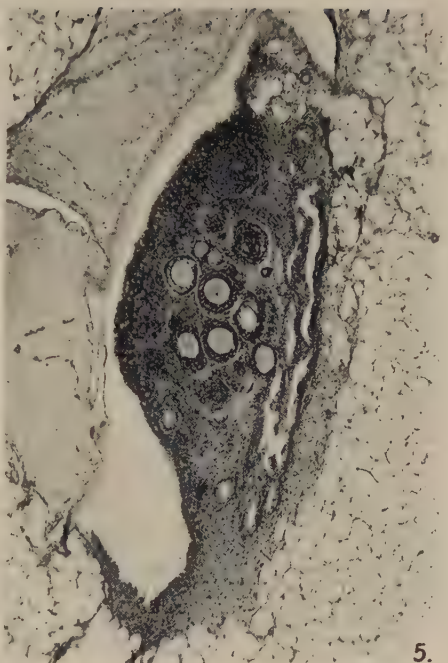
- 1 Female which had received testosterone propionate for the first 30 days of life. Digestive tract removed to show tremendously enlarged and convoluted uteri.
- 2 Cross section of normal uterus from 31-day-old female. 67 X.
- 3 Cross section of uterus from 31-day-old testosterone propionate treated female. Same magnification as normal uterus in figure 2. 67 X.



## PLATE 2

### EXPLANATION OF FIGURES

- 4 Normal ovary from 31-day-old female showing rete tubules. 67  $\times$ .
- 5 Ovary from 31-day-old testosterone propionate treated female. 67  $\times$ .
- 6 Efferent tubules from normal 31-day-old female. 85  $\times$ .
- 7 Efferent tubules from normal 31-day-old testosterone propionate treated female. Same magnification as normal efferents in figure 6. 85  $\times$ . This particular section represents the greatest development of the efferents found in the treated animals, although all others showed a greater development than the normal.





# FACTORS INFLUENCING LUNG LOBATION IN THE MOUSE

## I. GENETIC FACTORS: A PRELIMINARY REPORT <sup>1</sup>

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NINE FIGURES

The common house mouse, *Mus musculus*, was chosen as the experimental animal for this series of studies on factors influencing lung lobation because there were numerous inbred strains available to test the hypothesis that lung lobation may be influenced by genetic factors. Further studies in this series on non-genetic factors influencing the lobation will obviously be facilitated by the use of inbred strains.

Although there is an extensive literature, mainly of a descriptive nature, on the variations in lung lobation in man, there is none available on this subject in the mouse. The lack of literature may be attributed to the fact that most workers using mice in research are not interested in strictly morphological problems. Morphologists, on the other hand, have added little to the knowledge of lung lobation except a listing of the variations and anomalies found in man; these variants have of course been of phylogenetic interest to comparative anatomists. The proposed series of studies on the various factors influencing variation in the mouse should by analogy contribute to a better understanding of the variants in man.

The animals used for this study were discarded mice previously employed for various purposes by other workers.

<sup>1</sup> The author is indebted to the Roscoe B. Jackson Memorial Laboratory, Bar Harbor, Maine, which generously supplied the animals and the facilities for the study, subsequently continued as project No. 70 on a grant from the Medical Research Fund of the University of Oklahoma.

Most of them were of weaning age (4 to 6 weeks old). Mice of eight different inbred strains were used (the Jackson Memorial Laboratory strains C3H, C57, C57 br, dba, L, P, W, and Y). All strains were inbred by repeated brother-sister matings for at least twenty generations, and hence may be considered genetically uniform<sup>2</sup>. The specimens in strains L and C57 br, although obtained from autopsies, had non-pathological lungs. Mice of all other strains were healthy when killed for subsequent embalming.

The mice, killed with chloroform, were immediately preserved by injection into the thoracic and peritoneal cavities and through the foramen magnum into the brain. The embalming fluid used was a glycerol-phenol-alcohol mixture in the ratio of 1:1:1. The amount of injected fluid varied with the size of the mouse, averaging about 1 cc. Thoracic injections were made in the lateral line at the lower rib border to avoid puncturing the heart. All injections were made with a No. 27 hypodermic needle. After injection the mice were immersed in a large jar containing the same embalming fluid and kept 48 hours before dissection. After this length of time all the viscera were well fixed and easily dissected.

The lungs were exposed by radical dissection designed to permit visualization from all aspects — ventral, lateral, diaphragmatic, medial and dorsal. Sketches were made of all lung patterns, the simplified diagrams of which are shown in figures 1 to 9.

Nine distinct patterns were encountered during the course of the study. The most frequent of these patterns in all strains (except Y) consisted of four lobes on the right, one on the left. This pattern (pattern I, fig. 1) was therefore considered the normal one. Pattern II (fig. 2), which was in effect pattern I modified by a fissure in lobe 3, was the most common variation from the normal. Other patterns, III to IX, (figs. 3 to 9) occurred with relative infrequency in nearly all strains.

<sup>2</sup>For detailed information regarding these inbred stocks see "Biology of the Laboratory Mouse," by the staff of the Roscoe B. Jackson Memorial Laboratory, Blakiston, Philadelphia, 1941.

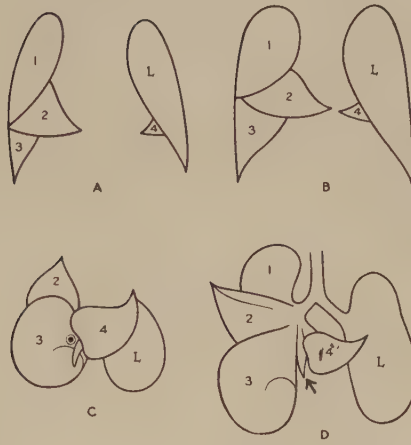


Fig. 1 Pattern I, the normal. A, ventral aspect; B, lateral aspect; C, diaphragmatic aspect; D, medial aspect, with lobes spread apart.

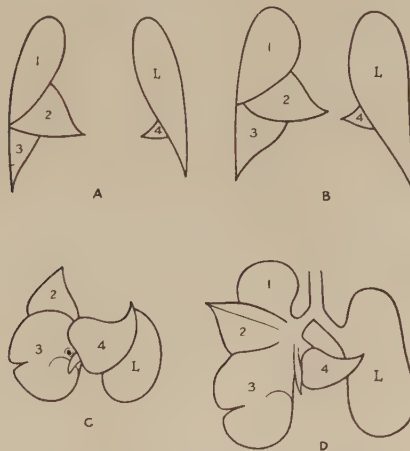


Fig. 2 Pattern II. Fissure in lobe 3, varying slightly both in extent and position.

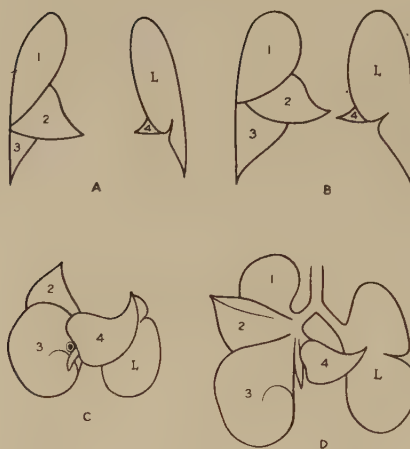


Fig. 3 Pattern III. Fissure in left lobe.

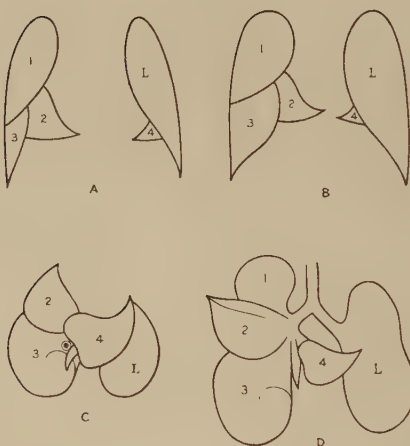


Fig. 4 Pattern IV. Lobe 2 overlaps lobe 3 on diaphragmatic surface; lobe 3 overlaps lobe 2 on ventral, lateral, and dorsal surfaces.

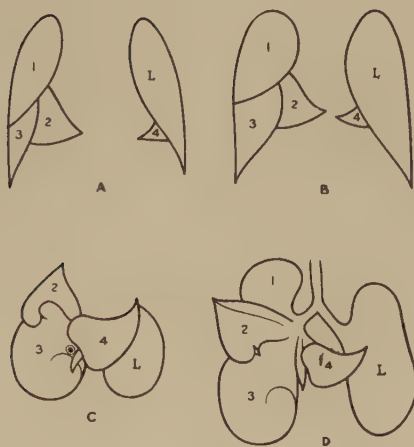


Fig. 5 Pattern V. Overlapping of lobes 2 and 3 on diaphragmatic surface; lobe 3 overlaps lobe 2 on ventral, lateral, and dorsal surfaces.

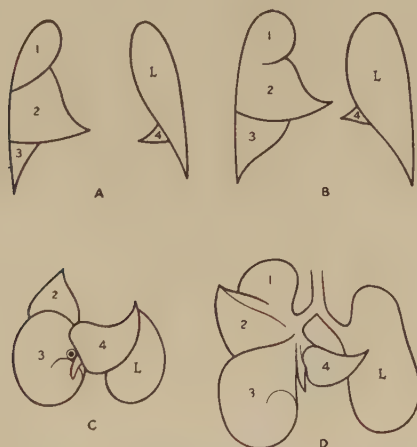


Fig. 6 Pattern VI. Incomplete fission between lobes 2 and 3.

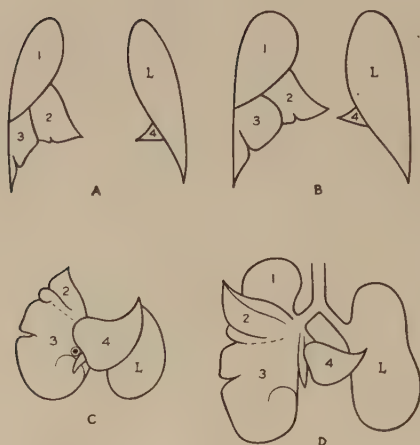


Fig. 7 Pattern VII. Incomplete fission (see dotted lines) between lobes 2 and 3 on diaphragmatic surface; fission complete on ventral, lateral, and dorsal surfaces; also fissures in lobes 2 and 3.

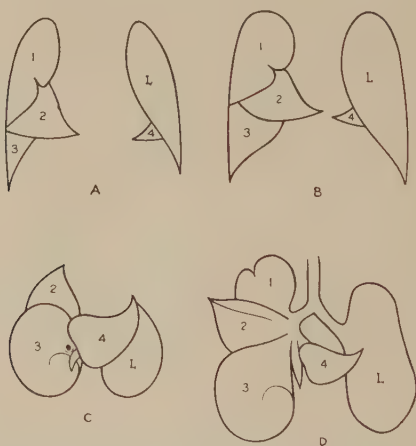


Fig. 8 Pattern VIII. Fissure in lobe 1.

A few specimens were found in which characteristics of several patterns were combined. Some variation in lobe 4 (the cardiac or infracardiac lobe) was found in all patterns. This variation in lobe 4 consisted of differences in size and disposition of a small lobule (marked by arrow, fig. 1) which was dorsal to the inferior vena cava. These minor variations are not here illustrated but were recorded in each instance.

Figures 1 to 9 show that with few exceptions (patterns VI, VII, figs. 6, 7) the variants of the normal pattern I are in the direction of fission rather than fusion of lobes. It is surpris-

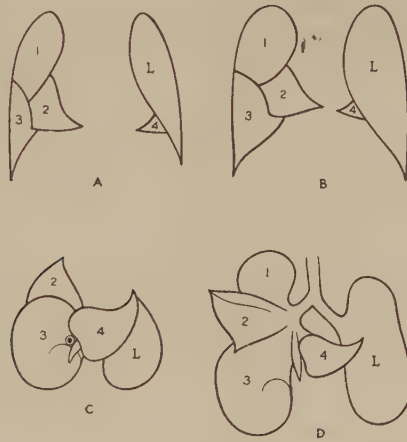


Fig. 9 Pattern IX. Lobe 3 overlaps lobes 1 and 2 on ventral, lateral and dorsal surfaces, in addition to normal overlap of lobe 2 on diaphragmatic surface.

ing, in view of this apparent fission tendency, that so few lungs are found with a fissure in the *left* lobe (pattern III, fig. 3). Also from phylogenetic reasoning more lungs of pattern III would have been expected, since two left lobes are of more frequent occurrence in mammals than are five right lobes. The occurrence of patterns, however, might have been considerably altered if other inbred strains than those selected had been used in the study.

Table 1 shows the incidence of each lung pattern in the strains studied. It is evident from this table, in spite of the small number of specimens of each strain (less than 100), that

there is a significant difference in the incidence of variation in different stocks. Thus, the C3H and P stocks show a low incidence of variation ( $5.5 \pm 3.1\%$  and  $3.3 \pm 3.3\%$  respectively), while the C57 and Y stocks show a much higher incidence ( $41.0 \pm 5.0\%$  and  $57.3 \pm 4.6\%$  respectively). Other stocks are intermediate between these extremes.

This study therefore demonstrates that (1) there are genetic factors influencing lung lobation in the mouse, since

TABLE 1

| STRAIN              | LUNG PATTERN |                 |                |                |   |    |     |      |    | TOTAL<br>NUMBER | VARIATION         |
|---------------------|--------------|-----------------|----------------|----------------|---|----|-----|------|----|-----------------|-------------------|
|                     | I            | II              | III            | IV             | V | VI | VII | VIII | IX |                 |                   |
| dba<br>(2 sublines) | 60           | 11              |                |                |   |    |     |      |    | 71              | $15.6 \pm 4.3\%$  |
| C3H                 | 51           | 1               | 1              |                |   |    | 1   |      |    | 54              | $5.5 \pm 3.1\%$   |
| C57<br>(4 sublines) | 56           | $35\frac{1}{2}$ | $\frac{1}{2}$  | $\frac{1}{2}$  | 3 |    |     |      |    | 67              | $41.0 \pm 5.0\%$  |
| L                   | 10           | 10              |                | 3              |   |    |     |      |    | 23              | $56.5 \pm 10.3\%$ |
| C57 br              | 11           | $1\frac{1}{2}$  |                | $2\frac{1}{2}$ |   |    |     |      |    | 15              | $26.6 \pm 11.4\%$ |
| P                   | 29           |                 |                | 1              |   |    |     |      |    | 30              | $3.3 \pm 3.3\%$   |
| W                   | 39           | $2\frac{1}{2}$  |                | $1\frac{1}{2}$ | 1 |    |     |      |    | 44              | $11.3 \pm 4.8\%$  |
| Y                   | 26           | $29\frac{1}{2}$ | $1\frac{1}{2}$ |                |   | 1  |     | 1    | 2  | 61              | $57.3 \pm 4.6\%$  |

Fractions indicate specimens showing characteristics of more than one pattern; e.g., one C57 specimen had characteristics of patterns II, III, and IV.

there are differences in the incidence of variation in different inbred stocks, and (2) the variation in lobation seems to be in the direction of fission rather than fusion of lobes.

Further studies on this problem are planned (1) to determine the type of bronchial tree characteristic of each pattern (especially patterns I and II), (2) to trace the process of development in a high-incidence strain and in a low-incidence strain in order to throw some light on the mode of action of the responsible genetic factors, (3) to analyze the type of inheritance involved in lung lobation in the mouse, and (4) to analyze the possible role of non-genetic factors influencing the lobation.

## SUMMARY

Variations in lobation of the lungs of mouse (*Mus musculus*) were studied in eight different stocks, each stock being genetically uniform as a result of prolonged inbreeding (twenty generations or more). Among these stocks were found nine distinct lung patterns, the variants from normal being mainly in the direction of fission rather than fusion of lobes. However, the incidence of variants in lobation was strikingly different in different stocks, from which circumstance it is concluded that genetic factors influence lobation of the lungs in mouse.



## VARIATIONS IN THE ORIGIN OF THE M. TRAPEZIUS<sup>1</sup>

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Except for the pectorals, the trapezius muscle is said to be more subject to deviation from "normal" than any other muscle (Bing, '02), and the anatomical literature is replete with instances of its anomalies. Nevertheless, to the best of our knowledge, there has been no systematic investigation of variation in the extent of the muscle.

The present study was carried out on eighty dissecting-room cadavers, constituting a mixed group of white and negro bodies, largely male<sup>2</sup>. For each of the 160 muscles the following features were noted: inferior level of vertebral origin; superior level of vertebral origin; span of attachment to the ligamentum nuchae; type of cranial origin, when present. There were many departures from the textbook description of a muscle arising from the superior nuchal line and external occipital protuberance, the ligamentum nuchae, and the vertebral spines and supraspinous ligament from the seventh cervical to the twelfth thoracic vertebra.

### OBSERVATIONS

*Extent of vertebral origin.* The lower limits of the muscles varied from the eighth thoracic to the second lumbar level. In table 1 are listed the number of specimens terminating at each vertebral spine. It will be observed that the left trapezius

<sup>1</sup>Contribution no. 365 from the Department of Anatomy, Northwestern University Medical School, Chicago, Illinois.

<sup>2</sup>That this number of specimens suffices for statistical review is indicated by the fact that frequency curves drawn for the data obtained were smooth in contour.

deviates more often from the "normal" inferior origin at the twelfth thoracic vertebra than does the right. There is perhaps some tendency for the muscle on the right to extend farther caudally than that on the left, but no confirmation of the statement that the former consistently reaches inferiorly beyond the latter (Bryce, '23; McMurrich, '30). The level of the eighth thoracic spinous process is by no means the highest reported for the lower limit of the trapezius, but we have not found any record of a muscle extending as low

TABLE 1  
*Lower extent of origin of 160 trapezius muscles.*

| VERTEBRAL LEVEL | RIGHT SIDE | LEFT SIDE  | TOTAL      |
|-----------------|------------|------------|------------|
| 8 T             | 2 ( 2.5%)  | 2 ( 2.5%)  | 4 ( 2.5%)  |
| 9 T             | 2 ( 2.5%)  | 4 ( 5.0%)  | 6 ( 3.8%)  |
| 10 T            | 15 (18.8%) | 17 (21.2%) | 32 (20.0%) |
| 11 T            | 23 (28.8%) | 25 (31.3%) | 48 (30.0%) |
| 12 T            | 32 (40.0%) | 25 (31.3%) | 57 (35.6%) |
| 1 L             | 5 ( 6.3%)  | 7 ( 8.8%)  | 12 ( 7.5%) |
| 2 L             | 1 ( 1.3%)  | 0          | 1 ( 0.6%)  |
|                 | <hr/> 80   | <hr/> 80   | <hr/> 160  |

as the second lumbar vertebra. Chudzinski (1898) was of the opinion that the trapezius never reaches past the twelfth thoracic vertebra. De Pina ('32) examined seventeen cadavers and encountered two trapezius muscles attaching to the eighth thoracic vertebra, four to the ninth, sixteen to the tenth, and twelve to the eleventh.

The upper limit of vertebral origin of the trapezius in our subjects agreed fairly well with the textbook "normal." Of 160 muscles, 130 (81.3%) had the seventh cervical vertebra as the highest level of spinous attachment, twenty-four (15.0%) the sixth cervical, and six (3.8%) the first thoracic (this distribution is undoubtedly only a reflection of the fact that, while the vertebra prominens is usually represented by the seventh cervical vertebra, it may be represented by the sixth cervical or first thoracic). In no case was any difference noted between the two muscles of the same body in this regard.

*Cranial extent of origin.* Table 2 shows the variation in the rostral reach of the muscles of our series. Asymmetry in this particular between the two muscles of a single cadaver occurred in only three instances. De Pina ('32) found the capital origin present in all the muscles of his series, in contrast with our finding of only 67.5% with cranial connections. Of 108 muscles attaining the skull, forty-three (39.8%) attached to the external occipital protuberance; thirty-six (33.3%) to the external occipital protuberance and superior nuchal line (the "normal"); fifteen (13.8%) to areas below the superior nuchal line; thirteen (12.0%) to the external occipital protuberance and regions below the superior nuchal

TABLE 2  
*Cranial extent of origin of 160 trapezius muscles.*

| VERTEBRAL LEVEL | RIGHT SIDE | LEFT SIDE  | TOTAL       |
|-----------------|------------|------------|-------------|
| 5 C             | 1 ( 1.3%)  | 1 ( 1.3%)  | 2 ( 1.3%)   |
| 4 C             | 2 ( 2.5%)  | 2 ( 2.5%)  | 4 ( 2.5%)   |
| 3 C             | 2 ( 2.5%)  | 3 ( 3.8%)  | 5 ( 3.1%)   |
| 2 C             | 4 ( 5.0%)  | 3 ( 3.8%)  | 7 ( 4.4%)   |
| 1 C             | 18 (22.5%) | 16 (20.0%) | 34 (21.3%)  |
| Skull           | 53 (66.3%) | 56 (68.8%) | 108 (67.5%) |
|                 | 80         | 80         | 160         |

line; and one (0.9%) laterally to the superior nuchal line alone, a type of origin noted by Poirier and Charpy ('12). The two muscles of a single body did not always have the same capital attachment, but differences, when present, were small, except in two cases, in which the muscle on one side gained the skull, while that on the other reached only to the first cervical spinous process. We cannot corroborate the opinion of Bryce ('23) that the right trapezius usually has a more extensive plaque of cranial origin than the left.

*Total extent.* The longest muscle of the series was one spanning twenty-one segments, from the skull to the second lumbar vertebra; the shortest, one covering eleven segments, from the eighth thoracic to the fourth cervical spine. The average number of segments covered was 17.6. Forty-eight instances

(30%) spanned eighteen segments, forty (25%) nineteen segments, and thirty-one (19.4%) seventeen segments. The three most common configurations of the muscle were: from the twelfth thoracic vertebra to the skull (thirty-eight specimens, 23.8%); from the eleventh to the skull (thirty-five specimens, 21.9%); and from the tenth to the skull (twenty-one specimens, 13.1%).

*Variations by side.* Of the eighty bodies, forty-nine (61.3%) showed differences between the muscles of the two sides, confirming the statements of LeDouble (1897), Poirier and Charpy ('12), and Bardeen ('33) that asymmetry is the rule. The inferior origins varied in thirty-three (41.2%), the superior in thirty-one (38.8%). Of the variations in the extent of caudal spinal origin, twenty-six (78.8%) were by one vertebral segment, seven (21.2%) by two segments. Of the thirty-one rostral variations, sixteen (51.6%) were by one segment, four (12.9%) by two segments, and eleven merely by attachment to different points on the skull. Of the forty-nine bodies in which the two trapezius muscles were not symmetrical, thirty-one (63.2%) exhibited divergence by one segment, nine (18.4%) by two, and two (4.1%) by three. In one case (2.0%) the discrepancies in level above and below cancelled one another so that each muscle covered the same number of segments. In six cases (12.3%), the differences between the two muscles were only in the range of cranial origin.

Of the forty-nine bodies showing dissimilarity in the span of the two trapezius muscles, fifteen (30.6%) presented differences above and below, thirty-four (69.4%) differences only above or below. Of the latter group, eighteen (36.8%) were at variance inferiorly, sixteen (32.6%) at variance superiorly. Evidently the trapezius muscles of a single body are more likely to differ in level at only one extremity than at both; the caudal and rostral limits of attachment are about equally variable.

*Anomalies.* In addition to dissimilarities between sides and the deficiencies met with in some specimens, one true anomaly was found, a slip extending from the tip of the arch of the

atlas to the deep surface of the muscle. This was probably a variety of the uncommon omo-transversarius. No aberrant fascicles of other sorts and no transverse inscriptions were encountered, which may give some idea of their rarity. Nor was any muscle seen in which any one of the three divisions of the trapezius, the dorso-scapularis inferior, dorso-scapularis superior and cleido-occipitalis, was separate from the others, though this is stated by LeDouble (1897) to be the most common abnormality of the muscle. One of us has had occasion to observe 925 consecutive dissecting-room subjects and has never seen a case of total absence or extreme deficiency. Such anomalies are therefore deemed exceedingly infrequent.

#### DISCUSSION

The variations found in this study make it probable that grave defects of the trapezius are merely rarer members of a progression from muscles longer than usual to complete lack. Such a sequence would include: muscles reaching the lumbar region; "normals"; muscles corresponding to our least extensive specimens; those of still shorter span; mere slips (Voltz, '04); and finally exceptional instances of absence (Limbeck, 1889; Schulze-Gocht, '28; Sheehan, '32; and Selden, '35). It may be pointed out that the most superior and most inferior origins are expansions occurring late in embryonic life (Bryce, '23), just as they are more recent in the primate line (de Pina, '32).

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# A STUDY OF THE PARATHYROID GLANDS OF THE NORMAL AND HYPOPHYSECTOMIZED MONKEY (MACACA MULATTA) <sup>1</sup>

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ONE TEXT FIGURE AND TWO PLATES<sup>1</sup> (FIFTEEN FIGURES)

Studies on the effect of hypophysectomy on the parathyroids have not been reported in monkeys or other primates, and even the normal structure of the parathyroids in these higher animals has not been described except for brief papers by Cowdry and Scott ('36) on the monkey and Arndt ('23) on the chimpanzee. Observations on these glands in monkeys are of interest not only because of the close phylogenetic relationship of monkeys to man, but also because the parathyroids (of at least *M. mulatta*) contain oxyphils, a cell type which has been found to be plentiful in the human except in early life. These glands in *M. mulatta* thus are structurally more similar to those of man than are the parathyroids of most other laboratory animals <sup>2</sup>.

Not only because of this characteristic but also because there is no agreement on the effects of hypophysectomy on the parathyroids, it seemed that it might be of value to undertake a study of the rather plentiful material available from the normal and experimental animals in this laboratory.

<sup>1</sup> Aided by a grant, administered by Dr. P. E. Smith, from the Rockefeller Foundation.

<sup>2</sup> Levine ('28) stated that oxyphils are present in the parathyroids of the cow and steer, and Houssay and Sammartino ('34) found an occasional oxyphil in the parathyroids of three operated but in no normal dogs. Arndt ('23) found a few oxyphils in the parathyroids of one of three chimpanzees.

A number of investigators have reported on the effects of hypophysectomy on the parathyroids in the common laboratory mammals. Atrophy was observed in the rat (Smith, '27) and dog (Koster, '30) and a possible slight atrophy in the rabbit (White, '33). On the other hand, Collip ('34) and Aschner ('12) saw no change in the rat and dog respectively. Collip ('34) observed enlargement of the parathyroids in one cat at the end of a 2-week postoperative period and suggested that pituitary ablation might be followed by a period of overactivity and, then, by one of atrophy.

Houssay and his collaborators described lesions in the parathyroids of twenty-five of thirty-eight dogs after hypophysectomy, in five of twelve after damage to the tuber cinereum, in all of three after hypophysectomy and thyroidectomy, in four of five after pancreatectomy, in all of six after hypophysectomy and pancreatectomy, and in three of thirty controls. These treatments led to a single type of lesion which varied in severity in different glands of the same individual, in time of appearance and in the number of glands involved in any one animal. The crucial experiment of repairing this damage by the administration of anterior pituitary extract failed, since it was still present in the parathyroids of four of six dogs so-treated ('34).

Houssay has consistently refused to use these findings as evidence for the secretion of a specific parathyrotropic factor, considering this to be only one possibility. Indeed, he believed that a nutritional disturbance produced by an absence of either the hypophysis or pancreas, and intensified when both glands were removed, was the most satisfactory explanation of this degeneration ('33). The loss of a hypophyseal growth or metabolic hormone with a general action on all organs was also suggested as a possible explanation.

#### MATERIAL AND METHOD

One or more of the parathyroids from sixty-two monkeys (*Macaca mulatta*) were used in this investigation<sup>3</sup>. Part of the animals had been injected with various endocrine products. The monkeys were grouped on the basis of sex and type of treatment.

<sup>3</sup> Doctor Smith performed the hypophysectomies and checked the completeness of the ablation by microscopic examination of complete serial sections of the pituitary region.

Only the external parathyroids were studied since the cost of a microscopic search for the internal and accessory glands was prohibitive. One external parathyroid was almost invariably located on the lateral side of each lobe of the thyroid. Although partly embedded in the thyroid gland, they were readily visible grossly. Their positions varied but were usually on the middle or upper one-third of the lateral lobes of the thyroid.

One external parathyroid from each monkey was fixed in Bouin's solution and the other in either Zenker-base (Zenker's fluid without acetic acid) or Champy's fluid. The glands were sectioned at  $3\mu$ ,  $4\mu$ , or  $6\mu$ . Those fixed in Bouin's fluid were stained with hematoxylin and eosin or the Severinghaus ('39) Altmann-Masson pituitary technique. The latter stain was used routinely after the other two fixatives and gave excellent results.

Three methods were employed in an attempt to detect any atrophy which might follow hypophysectomy. First, the volume of the Bouin-fixed parathyroid was determined by making outline drawings of every tenth section by means of a projection apparatus magnifying 100 times. After measuring the area of each drawing with a planimeter and correcting for magnification, the total volume in cu. mm. of each gland equalled  $\Sigma (\text{the area (sq. mm.)} \times 10 \times \frac{6\mu \text{ (or } 4\mu)}{1000})$ . Secondly, in each of the Zenker-base preparations, the various cell types and their nuclei were measured in the greatest diameter by means of an ocular micrometer. The recorded figure is the average diameter of twenty different cells or nuclei. Thirdly, cellular size was ascertained indirectly by counting the number of nuclei in an area measuring  $150\mu \times 150\mu$ . This area was outlined by small squares scratched upon a cover slip which had been placed in the ocular eye-piece. Counts were made in ten fields and averaged. All determinations were made on the  $4\mu$  sections of the Bouin-fixed gland, care being taken to select areas at the center of the section or near any adherent

thyroid tissue, since fixation seemed to have affected the size of the cells least in these places. The focus of the microscope remained unchanged during the counting.

Pale and dark oxyphils were counted in each of twenty high-power fields of the Zenker-base-fixed parathyroid and the average figure was taken as the oxyphil count for each type.

When Champy fixation was employed the gland was subsequently divided and one-half chromated for mitochondria and the other half osmicated for the Golgi apparatus, both according to the Severinghaus pituitary methods.

## RESULTS

### *The normal parathyroid*

The external parathyroids of the monkey were surrounded by a thin connective tissue capsule which was extremely delicate on the sides adjacent to the thyroid alveoli. The gland contained little connective tissue, a considerable quantity being found only around the larger blood vessels near the hilus. The writer has been unable to find any lumina which did not contain either connective tissue fibres or endothelial cells, thus, not being true acini, in contrast to Cowdry and Scott ('36) who described acini in the monkey parathyroid.

The parenchymal cells were compactly arranged, trabeculae and strands appearing only as a result of shrinkage by the fixation. Lobulation was rare.

Fat cells of varying sizes occurred singly and in small groups within or around the gland. The fat varied in amount and it is not possible to say that it increased with advancing age.

Inter-cellular colloid was sparse.

*Cell types.* The number of cell types which one may find in the parathyroid depends partly on the fixation and stain employed. Four types of cells were distinguished in material which had been fixed in the three fluids employed in this study.



*Pale principal cell.* The pale principal cell was the predominant type. Its nucleus was vesicular and was spherical, ovoid or somewhat irregular in shape. One or more nucleoli were present. Bouin fixation caused the cytoplasm to appear pale and to stain weakly with eosin or aniline blue. With the Severinghaus stain it was gray with a pink tone (blue light) after Zenker-base and blue after Champy's fluid.

Mitochondria were almost invariably present in well-fixed parathyroids. Although, in general, the mitochondria were distributed throughout the cell, they frequently accumulated in the portion of the cell bordering a capillary and, in this location, could be seen to be parallel to the long axis of the cell if not too densely massed. When a capillary was viewed in cross-section, the mitochondria in the apical parts of the surrounding cells formed a crown around it. A similar arrangement of mitochondria has been observed in the parathyroid of the horse by Bobeau ('11). The mitochondria were filamentous or rod-shaped. When filamentous they were sometimes grouped in clusters. Small enlargements occurred at varying intervals on the filaments.

The most prominent cytoplasmic structure after the mitochondria had been removed by fixation in Bouin's solution was a dark juxtanuclear body which stained grayish-blue with hematoxylin (figs. 4 and 12). When fixed in Champy's fluid the body took aniline blue and its structure was more clearly shown (fig. 2). It frequently appeared to be made up of threads which were somewhat parallel to each other. Usually, this organelle was compact and elongated with some lighter internal areas. Its position in the cell was not constant, being in the part of the cell either proximal or distal to the capillary or at the side of the nucleus. There frequently appeared to be two or more juxtanuclear bodies in the same cell but one could not always be certain that connecting portions had not been lost in sectioning.

The juxtanuclear body itself did not reduce osmium with osmication sufficient to demonstrate the Golgi body in other glandular tissue. It was blackened if the treatment was suf-

ficiently intense to blacken also the nuclear membrane and to turn the cytoplasm gray. However, this coloration was easily bleached out. The osmic Golgi technique (Nassonov-Kolatchev method) also failed to consistently impregnate any other structure of distinctive morphological characteristics, in this or the other cell types.

Within or closely adjacent to the juxtannuclear body one or more clear vesicles were frequently evident, especially after fixation in Bouin's and Champy's fluids. Typically they were elliptical, spherical or U-shaped, depending partly on the fixation (figs. 2, 4, 7 and 15), and frequently seemed to be formed by a partial splitting of the juxtannuclear body (fig. 2). The elliptical vesicle was situated at right angles to the long axis of the cell when located between the juxtannuclear body and the nucleus, or parallel to the long axis when located at the ends of more elongated cells. In some cases one could not be certain whether a vesicle was within or outside of the juxtannuclear body. Several discrete vesicles could sometimes be found within the same cell. Although clear areas formed by several adjacent vesicles were frequently of considerable extent after Bouin fixation, nevertheless, a cell which could be termed "wasserhelle" was found to be exceedingly rare.

Yellow bodies which seemed to be pigment were occasionally revealed in the principal cells by the use of Champy's fluid (fig. 2). Some of them measured as much as  $3\mu$  in diameter. They occurred most frequently in the parathyroids of large male monkeys.

*Dark principal cell.* This type possessed distinctive tinctorial characteristics and was definitely identified only after Champy fixation followed by the Severinghaus stain. It was much smaller than the preceding type and was pyramidal or elongated in shape. Both the nucleus and the cytoplasm stained a deep blue. The nucleus frequently extended the full width of the cell so that its lateral boundaries were difficult to distinguish from the cell membrane. The juxtannuclear body could usually not be identified. The mitochondria were never filamentous but were rod-like or granular. They never ac-

cumulated along the capillaries but were often rather abundant at the ends of the cell where they appeared to fuse into irregular masses.

*Dark oxyphil.* The term "dark oxyphil" as used here defines a cell which stained a deep red with acid fuchsin subsequent to Zenker-base fixation. The dark oxyphils tended to be larger than the principal cells, with nuclei slightly smaller, the average diameter of the cells being about  $12.9\mu$ , and of the nuclei,  $5.2\mu$ . Occasionally one was no larger than the smallest principal cells. The larger dark oxyphils were usually spherical in shape but when adjacent to a large pale oxyphil they were customarily flat or concave on that side. Their nuclei were structurally similar to those of the pale principal cells and pycnosis was rare.

The cytoplasmic background of this cell after Champy fixation was of two varieties. In some cells it was light blue and similar to that of the pale principal cell (fig. 16); in others it was a deep blue resembling more that of the dark principal cell (fig. 7). Some of the cells with a dark blue background were completely filled with a bright red, rather homogeneous material which had the appearance of coalesced mitochondrial substance (fig. 15). The juxtanuclear body was apparent in many of these cells, especially those of the former group.

In Champy-fixed material this cell type was seen to be filled to a variable degree with mitochondria which were of varied shapes and sizes. They were less osmiophilic than the mitochondria of the principal cells. Some cells were so packed with mitochondria that blue cytoplasm could not be discerned. That the organelles which stained with the acid fuchsin of the Severinghaus technique were mitochondria and not oxyphil granules, was indicated by the fact that after fixation in Bouin's solution no similar structures could be stained with acid fuchsin when followed by aniline blue, even if the slide was steamed repeatedly with acid fuchsin and weakly decolorized in distilled water.

*Pale oxyphil.* When fixation in Zenker-base solution was followed by the Severinghaus stain, this cell stood out in sharp contrast to all other types by virtue of its large size and pale granular cytoplasm. Its nucleus was usually small and eccentrically placed (fig. 13). The average diameter of the pale oxyphil was about  $15\mu$  and of its nucleus, approximately  $4.7\mu$ . Occasionally one was as small as the pale principal cells. Typically the cell was spherical and packed with granules. Structures suggestive of the juxtannuclear body were infrequently observed. After Champy fixation the granules stained with aniline blue (fig. 5) and the mitochondria were sparsely scattered and tended to be spherical or rod-like.

Particularly puzzling was a cell type which was clearly defined only by Champy fixation. It was obviously in the oxyphil line, reaching the size of the largest pale oxyphils (fig. 8). This cell differed from the pale oxyphil as described above in that its cytoplasm usually contained clear areas. However, the existing cytoplasm was made up of blue granules which were of about the same size as the mitochondria. The latter reached a comparatively large size and possessed varied shapes. Occasionally portions of the periphery of the individual mitochondria stained red and the remainder dull pink with acid fuchsin. They also sometimes blackened intensely with  $\text{OsO}_4$ . Large vacuoles occurred in the cytoplasm.

The correlation of these cell types with those observed after Bouin fixation is difficult. After Bouin's fluid, large cells were present, in some of which the cytoplasm was reticular whereas, in others, it was composed almost entirely of granules which stained with both eosin and aniline blue (fig. 14). The most logical deduction seems to be that those cells with a reticular, eosinophilic cytoplasm were the mitochondria-packed dark oxyphils of Champy and Zenker-base fixations while the granular cells were the pale oxyphils.

The distribution of oxyphils was different from that found in the human in that they were rather evenly scattered throughout the parathyroid and rarely found in groups. Also, the dark oxyphils exceeded the pale oxyphils in number.

Mitotic figures were extremely rare in the parathyroid only three having been observed in all of the material examined. Similar observations have been made in the human (Bergstrand, '19; Morgan, '36; Castleman and Mallory, '35), in the horse (Bobeau, '11), and in the monkey (Cowdry and Scott, '36).

*Cell relationship.* It is not possible to make definite statements concerning cell transitions from this material. It may be possible when a method of experimentally altering the cytological picture of the parathyroid gland is available, but hypophysectomy is not such a method. On the basis of variations in the mitochondria, cellular and nuclear size, granulation and intensity of coloration, a cycle of cell transition can be suggested.

The pale principal cell, by virtue of its number, must be considered the basic type. It appeared to change into dark oxyphils through an accumulation of mitochondria and enlargement of the cell, transitional forms being easily found after both Zenker-base and Champy fixations. The dark oxyphils with the pale blue cytoplasm were, in reality, probably principal cells filled with mitochondria in which granules had not yet developed (fig. 16). As the granules formed, the cell seemed to become more spherical in shape and the cytoplasmic background to stain more deeply with aniline blue (fig. 7).

Transitional forms were also observed between the pale and dark oxyphils, in fact, when Champy's fluid had been used, the observer was frequently embarrassed by his inability to classify these cells. After Zenker-base fixation, cells intermediate in color between the pale and dark oxyphils were present in which the pale granulation was easily observed (fig. 13). Thus it would appear that as the mitochondria of the dark oxyphil disappeared, granules accumulated forming the pale oxyphil. This transition resembles that described for the human parathyroid by Morgan ('36). Hunter and Turnbull ('31) stated that the two types are related. It is of further interest to observe that the average diameter of the nucleus became progressively less while the average diameter of the

cell increased as one passed from the pale principal cell to the dark oxyphil to the pale oxyphil.

Finally, very dark blue cells containing few mitochondria after Champy fixation, could be seen in some glands to vary from the size of the largest pale oxyphils to that of the small principal cells. These were rare and when fixed in Zenker-base solution would probably have been classed as small pale oxyphils. They were possibly undergoing degranulation and could, then, establish a relationship between the pale oxyphils and principal cells.

After Champy fixation, cells which were intermediate in size, shape and intensity of coloration with aniline blue between the dark and pale principal cells appeared to relate these two types and possibly to connect the degranulating pale oxyphils with the pale principal cells.

Both the dark principal cell and the dark oxyphil seen after Bouin fixation showed some characteristics typical of degeneration. In some cases the former type was extremely narrow and distinguishable from the intercellular stroma with difficulty. The eosinophilic granules of the pale oxyphils, after Bouin fixation, seemed to fuse, forming a red homogeneous cytoplasm enveloping a pycnotic nucleus (fig. 9). This change would agree with the colloidal degeneration of the human oxyphils described by Gilmour ('39).

#### *The effects of hypophysectomy*

*Volume.* In both sexes a slight atrophy was indicated after hypophysectomy by the absolute volumes of the parathyroids and by the ratios of volume to body weight. The parathyroids of the normal females averaged 1.48 cu. mm. (ratio of .344 cu. mm. per kilogram) as compared with 1.08 cu. mm. (ratio of .273) for the hypophysectomized animals (table 1). Those from comparable groups of males averaged 1.72 cu. mm. (ratio of .276) and 1.35 cu. mm. (ratio of .244) respectively.

Among the females, the only possible evidence of stimulation by hormonal treatment was furnished by the volume of the parathyroids from four ovariectomized females treated

TABLE 1  
*The effect of hypophysectomy on the size of the parathyroid and its principal cells.*

| TREATMENT                  | NO. OF<br>MONKEYS | BODY WEIGHT<br>(KG.) | DAYS<br>OPERATED | SIZE OF PRIN. CELLS ( $\mu$ ) |         | VOL. OF PARAT.<br>(CU. MM.) | VOL. (CU. MM. PER<br>KG. BODY WT.) |
|----------------------------|-------------------|----------------------|------------------|-------------------------------|---------|-----------------------------|------------------------------------|
|                            |                   |                      |                  | Cell                          | Nucleus |                             |                                    |
| (A) FEMALES                |                   |                      |                  |                               |         |                             |                                    |
| Normal                     | 7                 | 3.9-6.9              |                  | 8.7                           | 5.6     | 1.48 (1.05-2.54)            | .344 (.152-.643)                   |
| Inc. hyp.                  | 3                 | 4.1-4.8              | 6-47             | 8.6                           | 5.5     | 1.24 (1.2-1.3)              | .275 (.256-.292)                   |
| Hyp.                       | 6                 | 3.5-4.7              | 26-206           | 8.1                           | 5.5     | 1.08 (.054-2.18)            | .273 (.116-.589)                   |
| Hyp., estrogen             | 4                 | 2.8-4.7              | 25-187           | 8.2                           | 5.2     | 1.02 (0.89-1.18)            | .241 (.191-.291)                   |
| Hyp., progesterone         | 3                 | 3.4-4.0              | 55-336           | 8.3                           | 5.4     | 1.37 (1.09-1.78)            | .361 (.309-.456)                   |
| Miscellaneous <sup>1</sup> | 12                | 3.2-6.0              | 15-395           | 8.6                           | 5.4     | 1.43 (0.52-2.66)            | .312 (.112-.830)                   |
| (B) MALES                  |                   |                      |                  |                               |         |                             |                                    |
| Normal                     | 6                 | 3.0-11.3             |                  | 8.9                           | 5.7     | 1.72 (0.88-3.16)            | .276 (.181-.325)                   |
| Inc. hyp.                  | 2                 | 3.5-5.4              | 25-75            | 7.8                           | 5.2     | 1.21 (0.86-1.57)            | .263 (.245-.281)                   |
| Hyp.                       | 5                 | 4.0-7.2              | 35-160           |                               |         | 1.35 (0.90-2.15)            | .244 (.151-3.13)                   |
| Hyp., PMS                  | 1                 | 9.8                  | 45               | 9.2                           | 5.5     | 3.42                        | .348                               |
| Hyp., testosterone         | 2                 | 5.6-6.7              | 19               |                               |         | 1.29 (0.84-1.74)            | .204 (.150-.258)                   |
| Miscellaneous <sup>2</sup> | 9                 | 3.8-9.7              | 3-105            | 8.5                           | 5.4     | 1.9 (1.31-2.82)             | .291 (.233-.602)                   |

Inc.—incompletely. Hyp.—hypophysectomized.

<sup>1</sup>Includes estrogen-treated incompletely hypophysectomized and non-operated monkeys, and estrogen- or progesterone-treated and non-treated ovariectomized monkeys.

<sup>2</sup>Includes androstenedione-treated incompletely hypophysectomized monkeys, estrogen- or testosterone-treated non-operated monkeys, and estrogen-treated and non-treated castrates. When an effect may have been elicited by the administration of these hormones to the individuals of the miscellaneous groups, dosages are given in the text.

TABLE 2  
Summary of treatments given monkeys listed in table 1.

| GROUP                                      | NO. OF<br>MONKEYS | TREATMENT                                                                 | DAILY<br>DOSE                                  | DAYS<br>TREATED |
|--------------------------------------------|-------------------|---------------------------------------------------------------------------|------------------------------------------------|-----------------|
| (A) FEMALES                                |                   |                                                                           |                                                |                 |
| Hypophysectomized                          | 2                 | Desoxycorticosterone acetate                                              | 25 mg.                                         | 21 & 25         |
|                                            | 1                 | Estradiol benz. (6 day interval<br>before autopsy)                        | 400 i. u.                                      | 10              |
| Hypophysectomized,<br>estrogen-treated     | 3                 | Estradiol benz. (Progynon-B)                                              | 400 i. u.                                      | 5, 10 & 13      |
|                                            | 1                 | Estradiol benz.                                                           | 1000 i. u.                                     | 12              |
| Hypophysectomized,<br>progesterone-treated | 1                 | Progesterone <sup>1</sup>                                                 | 10 mg.                                         | 3               |
|                                            | 1                 | Progesterone                                                              | 5 mg.                                          | 8               |
|                                            | 1                 | Progesterone                                                              | 1 mg.                                          | 10              |
|                                            |                   | Gonadin                                                                   | 25-100 u.                                      | 7               |
|                                            |                   | Pregnancy urine (Synapoidin)                                              | 5 cc.                                          | 1               |
| (B) MALES                                  |                   |                                                                           |                                                |                 |
| Hypophysectomized                          | 1                 | PMS <sup>2</sup> (Upjohn and Schering)<br>(8 day interval before autopsy) | 200 Saunders u.<br>5800 Cartland u.<br>(Total) | 39              |
| Hypophysectomized,<br>PMS-treated          | 1                 | PMS (Upjohn)                                                              | 300 r. u.                                      | 26              |
| Hypophysectomized,<br>testosterone-treated | 2                 | Testosterone (Perandren)<br>Eschatin                                      | 500 i. u.<br>1 cc.                             | 18              |

<sup>1</sup> All progesterone preceded by treatment with estradiol benzoate (Progynon-B).

<sup>2</sup> Pregnant mare serum.

with rather heavy doses of estradiol benzoate (400 to 2000 i. u. daily for 8 to 14 days). These glands averaged 1.87 cu. mm. (ratio of .488) and are included within the miscellaneous group (table 1). Progesterone appeared to have had some effect on the hypophysectomized females.

The parathyroid of one hypophysectomized male treated with pregnant mare serum was large (table 1). Testosterone treatment of two non-operated males (included in the miscellaneous group) in doses of 25 mg. per day for 19 and 25 days may have caused some enlargement, the average volume being 2.29 cu. mm. (ratio of .418).

As indicated by the absolute volumes, the parathyroids of the males were generally larger than those of the females but when considered on the basis of relation to body weight the reverse seemed to be true. This relationship was especially evident when attention was limited to the normal animals only.

*Size of cells.* The principal cell is the most important type to be considered under this heading since it was predominant in number. This cell and its nucleus were very slightly smaller in the hypophysectomized females than in the normals, the average measurements being  $8.1\ \mu$  (nucleus,  $5.5\ \mu$ ) and  $8.7\ \mu$  (nucleus,  $5.6\ \mu$ ), respectively (table 1). Comparable data were not available from the males. In view of the small number of dark and pale oxyphils present it would seem to be unwise to attach significance to the small differences in size of these cells in the various groups.

Similarly, significant reduction in cellular size was not indicated by the nuclear counts. Although the average count of 255 for the hypophysectomized females was somewhat higher than the 196 of the normals, the ranges of the two groups showed a marked overlapping being 211–320 and 138–303, respectively. There were no variations worthy of notice in any other groups of this sex. Adequate data were not available from the males whereby one could observe the effects of hypophysectomy alone. The average counts in all groups of adequate size varied from 214–276. Two hypophysectomized male monkeys which had received pregnant mare

serum, in one of which the injections were stopped 8 days before autopsy, gave counts of 198 which were on the lower side of the range of the normal group. In general, it may be said that the average diameter of the principal cells bore an inverse relationship to the nuclear count even though the two determinations were done on glands fixed by different methods.

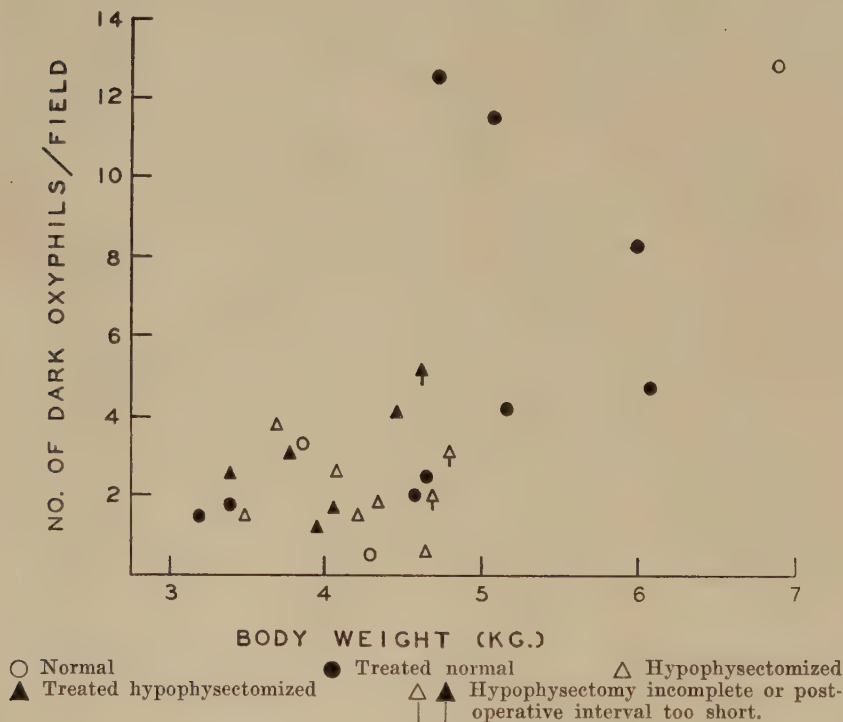


Fig. 1 The relationship of body weight to the number of dark oxyphils in the parathyroids of female monkeys.

*Oxyphils.* The number of dark oxyphils increased in direct proportion to the body weight. This is graphically shown for the females in figure 1. A similar plotting of the oxyphil counts for the males demonstrates the same relationship with a much greater spread in the higher weight ranges. One is, in reality, probably comparing the number of oxyphils with

age and it seems likely that there was a greater variation in age among the heavier males. One of the two males with an oxyphil count of over forty was known to be extremely old. A comparison of the number of oxyphils in a light male, My 591, with the number in heavier males (table 3) also emphasizes this correlation of body weight with the number of oxyphils.

TABLE 3  
*Incidence of various cell types in normal and hypophysectomized males, treated and untreated*<sup>1</sup>

| MY.              | BODY WEIGHT (KG.) | DAYS HYP. | TREATMENT                  | PALE PRINC. CELLS | DARK PRINC. CELLS | DARK OXYPHILS  |                | PALE OXYPHILS |
|------------------|-------------------|-----------|----------------------------|-------------------|-------------------|----------------|----------------|---------------|
|                  |                   |           |                            |                   |                   | Dark cytoplasm | Pale cytoplasm |               |
| 662              | 12.7              |           |                            | 88.4              | 0.50 <sup>1</sup> | 0.50           | 0.30           | 0.70          |
| 663              | 11.8              |           |                            | 103.3             | 1.85              | 0.55           | 1.15           | 0.05          |
| 664              | 7.4               |           |                            | 115.7             | 1.25              | 0.25           | 2.65           | 0.70          |
|                  |                   |           | Average                    | 102.4             | 1.20              | 0.43           | 1.36           | 0.48          |
| 660              | 9.8               | 45        | PMS                        | 99.1              | 1.25              | 0.20           | 0.85           | 0.55          |
| 597 <sup>2</sup> | 6.8               | 117       |                            | 83.7              | 1.30              | 0.20           | 0.60           | 0.10          |
| 598 <sup>3</sup> | 8.0               | 348       |                            | 158.2             | 2.65              | 1.00           | 1.10           | 0.75          |
|                  |                   |           | Average                    | 120.9             | 1.97              | 0.60           | 0.85           | 0.42          |
| 657              | 8.43              |           | Estradiol benzoate implant | 119.2             | 1.60              | 0.35           | 0.50           | 0             |
| 591              | 3.82              |           | Testosterone               | 99.6              | 0.70              | 0.05           | 0              | 0.1           |

<sup>1</sup> Each recorded figure is the average number of cells in twenty oil immersion fields selected at random. Champy fixation. Severinghaus Altmann-Masson stain.

<sup>2</sup> Treatment with PMS and androstenedione stopped 8 days before autopsy.

<sup>3</sup> Treatment with extract of sheep AP stopped 13 days before autopsy.

When the relationship of general body weight to the number of oxyphils is considered, it becomes evident that none of the various treatments here employed has significantly affected the incidence of these cells. This is borne out in the case of the females by figure 1 where all points are grouped along the same curve. The pale oxyphil count ranged from 0.05 to 1.0 and showed no significant variations in any group.

An examination of table 3 will show that the number of dark oxyphils, pale oxyphils, dark principal cells and pale

principal cells found in two non-treated hypophysectomized males after Champy fixation was not markedly different from the average number in three controls.

*Structure.* Zenker-base fixation was used almost exclusively for cytological study of the parathyroids of the females. This method enables one to observe the quantity but not the form of the mitochondria. With the exception of one hypophysectomized monkey they were found to be present in practically all principal cells regardless of type of treatment administered. One parathyroid from one female, hypophysectomized for 318 days, was fixed in Champy's fluid and showed prominent mitochondria which were rather evenly distributed throughout the cells and rarely accumulated along the capillaries.

A comparison of Champy-fixed parathyroids from two non-treated hypophysectomized males and from one pregnant mare serum-treated male, with those from three controls (table 3) failed to reveal any change in form, number or distribution of mitochondria in the pale principal cells.

The juxtannuclear body was normally present in practically all pale principal cells and although more conspicuous in some individuals than others, its prominence was not consistently influenced by any treatment employed. This structure was noted as being unusually prominent in three of the ovariectomized females which were treated with estrogens. The accompanying vesiculation of the cytoplasm similarly showed no consistent variations. The connective tissue fat remained unaffected.

*Degeneration.* It has been demonstrated in the rat (Jackson, '16; Hoskins, '24) and in man (Gilmour, '39) that a darkening of the cytoplasm with increased eosinophilia frequently appears in the principal cells. These authors believed that drying or compression prior to fixation was the causative factor. Similar cells have been repeatedly seen in the monkey after Bouin and Champy fixations. They occurred almost exclusively at the periphery of the gland especially at the free surface, but sometimes extended towards the center in strands.

Besides having a cytoplasm which was strongly eosinophilic, this type of cell was shrunken and the nucleus was dark. In general, these cells were of as frequent occurrence in the controls as in the experimentals. In only two cases, one of which was a progesterone-treated hypophysectomized female, did they occur at the center of the gland where their presence could hardly be accounted for on the basis of compression or drying.

There was no constant and unquestionable degeneration of the parathyroids after hypophysectomy. Pyknosis and vacuolization occurred occasionally regardless of type of treatment. The parathyroids from the non-treated hypophysectomized males were normal; those from two of the hypophysectomized females showed questionable signs of breakdown. In no case were these changes as severe as those described by Houssay and Sammartino ('34) in the dog.

#### DISCUSSION

*The oxyphils.* Since it has now been demonstrated that in the parathyroids of both the horse (Bobeau, '11) and monkey, cells may be filled with mitochondria, it is unwise to assume that all cytoplasm which stains with acid fuchsin or eosin is composed of oxyphil granules unless control material is available in which a fixation has been employed which will remove the mitochondria. For example, the fixatives most commonly employed in studies of human parathyroids contain either formalin or chromic acid both of which aid in the preservation of mitochondria. Even when acetic acid is added to Zenker-base solution it cannot be depended upon to remove these bodies. Morgan ('36) fixed human parathyroids in Zenker's fluid, stained with an acid fuchsin-aniline blue stain and concluded that dark oxyphils are filled with "bright cherry-red masses" of granules. He also frequently found "... dark principal cells with just a few granules in the cytoplasm which cannot be definitely classified with the oxyphil series." He did not consider the possibility that this fuchsinophilic material might be mitochondrial substance. Morgan

concurred in the conclusion of Hunter and Turnbull ('31): "The appearances suggest that the oxyphil cells are principal cells in which the cytoplasm has been so charged with oxyphil granules that the basophil net has been more or less reduced to a limiting membrane".

In view of these statements, it is of interest to observe that, in the monkey, the only granules which were retained after fixation by a fluid containing acetic acid and no chromic acid (Bouin's solution), took aniline blue and eosin and would not stain differentially with acid fuchsin if followed by aniline blue. It was evident, especially after Bouin or Champy fixation that the granular cytoplasm of the pale oxyphils was not always strikingly different from the cytoplasm of the principal cells in staining capacity.

Investigators have expressed varied opinions on the physiological importance of the oxyphil. Some of the earlier workers believed that the cell was packed with secretory granules and was, therefore, in a state of high activity. The pale oxyphil has been regarded as undergoing a type of colloidal degeneration to form a dark oxyphil which ultimately fragments (Bergstrand, '19; Gilmour, '39), as being the "ripened" cell which finally degenerates (Marine, '32) and as being capable of producing an excessive or abnormal secretion (Morgan, '36).

This investigation of the monkey parathyroid indicates that, when a method which will demonstrate mitochondria is used, the dark oxyphils must be subdivided into two groups. One of these groups includes cells filled with mitochondria and possessing normal nuclei which in every respect resemble the nuclei of pale principal cells (figs. 7, 13 and 15). On cytological grounds one could not designate this cell as having undergone degeneration. The second type of dark oxyphil was exceedingly rare in the monkey and possessed a homogeneous, colloid-like, eosinophilic cytoplasm after Bouin fixation (fig. 9), and probably corresponded to a cell with an orange cytoplasm after Champy fixation (fig. 6). The nucleus was usually pycnotic and this cell was probably degenerative

and may be the dark oxyphil frequently observed in the human. Both Morgan ('36) and Castleman and Mallory ('35) stated that the nucleus of their dark oxyphil was hyperchromatic.

*Juxtannuclear body.* In so far as the author is aware only two references have been made to the juxtannuclear body in the literature. Pappenheimer and Wilens ('35) mentioned its presence in man; Cowdry and Scott ('36) called this structure in the rhesus monkey a "basophilic body". The latter authors were hesitant to establish a homology between the basophilic body and the juxtannuclear body of the human parathyroid. Dr. Pappenheimer has kindly examined some of our preparations and in his opinion the same organelle is under consideration in both instances. Therefore, it seems advisable to use the terminology first employed by Pappenheimer and Wilens.

Inasmuch as none of the treatments employed significantly affected the juxtannuclear body, no definite statements concerning its function can be made.

*Hypophysis-parathyroid relationship.* In order to evaluate these data fairly, one must consider the many difficulties inherent in a quantitative study of the parathyroids. A number of reports have emphasized the variability in number and location of these glands in several species as well as the variations in size of different glands in the same individual. Furthermore, the parathyroids are so small that weighing before fixation is impractical and, in consequence, it is necessary to resort to the less satisfactory method of reconstruction. Because of these difficulties no one has, heretofore, employed an objective method in studying the effects of hypophysectomy on the size of the parathyroids of the mammal.

Volumetric determinations, nuclear counts and cell measurements all indicated a slight atrophy of the parathyroids of the monkey after hypophysectomy. However, the structure of the cells and the distribution of cell types were normal. It would seem to be illogical to attribute the occasional evidences of degeneration to a loss of parathyrotropic substance

since they were entirely absent in hypophysectomized males and were irregular in appearance and not severe in the hypophysectomized females. Indeed the structure of the gland indicates that its function has not been impaired. Although Evans ('33) found a lowered serum calcium after hypophysectomy in rats, Collip ('34) reported a slight increase and a negative calcium balance. Mazzocco ('27) and Gerschman and Marenzi ('35) found no changes in serum calcium in hypophysectomized dogs.

The possibility that the pituitary may act on the parathyroids through the gonads must be kept in mind. It has been shown that the parathyroids of the human female are 22% heavier than those of the male during the period of sexual activity (Pappenheimer and Wilens, '35) and that they are probably also larger in the female rat (Jackson, '16). Castration of the male albino rat has no effect on their size (Overholser, '29). The literature dealing with the effects of estrogen on the blood calcium has been recently reviewed by Levin and Smith ('38). These workers concluded from their own investigations that the blood calcium of rabbits is not significantly influenced by estrogens.

This study has shown that the absolute volume of the parathyroids of female monkeys was less than that of the males. However, when considered on the basis of volume of parathyroid per kilogram of body weight, the glands of the females were larger. In only the ovariectomized females treated with rather heavy doses of estrogen was there any indication of parathyroid stimulation resulting from the injection of female sex hormone. A stimulative effect by progesterone in the females and by testosterone in the non-operated males is possibly suggested by the data. Testosterone, as used, had no effect on the parathyroids of hypophysectomized males. These data are not sufficiently extensive to permit final conclusions.

The injection of anterior pituitary extracts has been reported to induce histological changes in the parathyroids of the rabbit (Hertz and Kranes, '34; Anselmino et al., '35), cat, guinea pig (Anselmino et al., '35), rat (Anselmino et al., '34)

and dog (Anselmino et al., '35; Ham and Haist, '39). The only effect common to all of these forms was cellular enlargement, accompanied in some cases by hyperemia and hyperplasia. These structural changes were interpreted to represent the result of stimulation.

It has also been claimed that treatment with pituitary extracts will raise the blood calcium level of rats (Hoffman and Anselmino, '34; Friedgood and McLean, '37), dogs (Hoffman and Anselmino, '34) and of cats (Shapiro, '34). Teel and Watkins ('29) found no rise in the dog and Hogben and Charles ('32) observed a drop in the blood calcium level of cats.

In view of these positive reports of hypophyseal action on the parathyroids and of the possible slight atrophy of these glands after hypophysectomy in the monkey, any conclusion concerning pituitary control must be made with reservations. It can be stated that if a hypophyseal parathyrotropic factor does exist, it is not comparable in significance in the adult animal to those principles governing the activity of the thyroid, adrenal cortex and gonads.

#### ACKNOWLEDGMENTS

I wish to express my appreciation to Drs. P. E. Smith and A. E. Severinghaus for the advice which they have given in this study.

#### SUMMARY

1. The parathyroids of the monkey contained the following cell types when studied by the methods used in this investigation: pale principal cells, dark principal cells, dark oxyphils and pale oxyphils.

2. The majority of dark oxyphils, as defined, were essentially mitochondria-filled cells which increased in number in direct proportion to the body weight.

3. The cytoplasm of the pale oxyphil was filled with granules which stained with aniline blue after Champy and Bouin fixations, and were very lightly stained after Zenker-base fixation.

4. The juxtannuclear body was visible in the cytoplasm of practically all principal cells and in some dark oxyphils. It was composed of fine thread-like structures. Within it, or near it, clear vesicles were sometimes found.

5. The mitochondria were filamentous or rod-shaped in the principal cells, being more delicate in the pale than in the dark principal cells. They were frequently large and spherical in cells of the pale oxyphil line.

6. Hypophysectomy of male and female monkeys resulted in a possible slight atrophy of the parathyroids as indicated by direct measurement of cells, nuclear counts and volumetric determinations of the glands.

7. Hypophysectomy was without significant effect on the mitochondria, juxtannuclear body and distribution of cell types.

8. The parathyroids of the normal females in this colony were larger than those of the males only after allowance was made for the difference in body weight.

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## PLATE 1

## EXPLANATION OF FIGURES

2 Drawing of a pale principal cell. The juxtannuclear body with its parallel parts is present at the lower left. The elongated light area in the center of this structure is an elliptical vesicle and a U-shaped vesicle surrounds the right portion of the juxtannuclear body. The spherical body at the upper left of the nucleus is yellow and is believed to be pigment. Filamentous mitochondria are scattered throughout the cell and have accumulated along the intercellular space. Monkey 662 ♂. About  $\times 2200$ . Champy.  $3\mu$ . Severinghaus Altmann-Masson.

3 Drawing of a principal cell after fixation with Zenker-base solution. The juxtannuclear body caps the nucleus. A small piece of it is present in the lower left hand corner surrounded by dark mitochondria. Monkey 639 ♀. About  $\times 3800$ .  $4\mu$ . Severinghaus Altmann-Masson.

4 Drawing of a principal cell after Bouin fixation. This shows the dark juxtannuclear body at the right and the clear vesicles which form beside it. Projections from the body seem to partially surround the vesicles. Monkey 639 ♀.  $4\mu$ . Harris' hematoxylin and eosin.

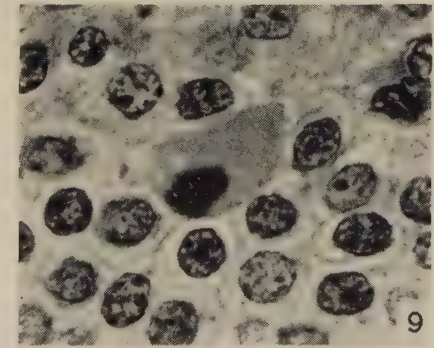
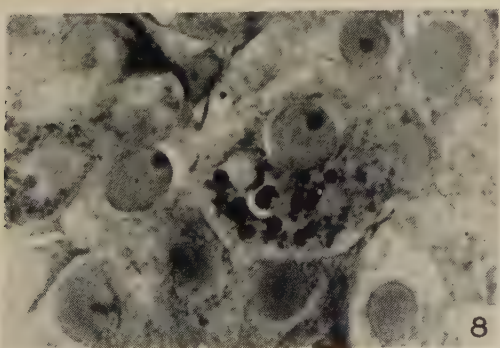
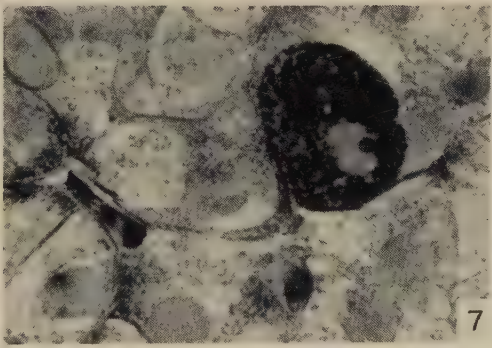
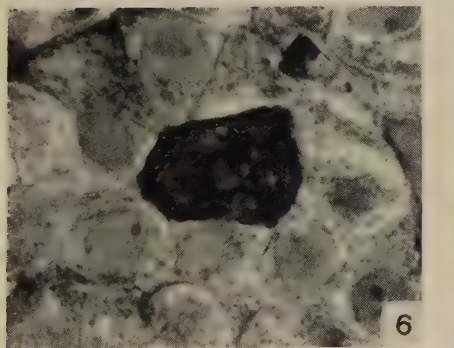
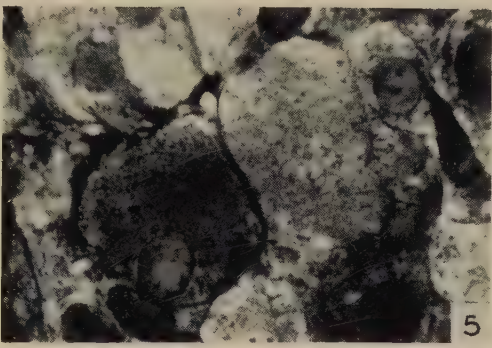
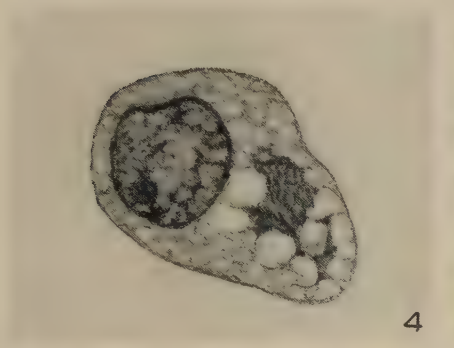
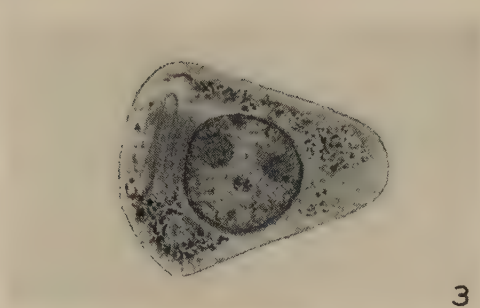
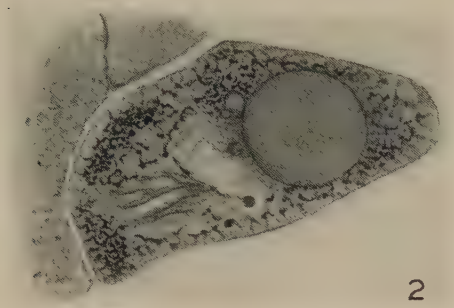
5 Two large pale oxyphil filled with pale blue granules and containing a few small granular mitochondria. Note the spherical shape of the cell and eccentric position of the nucleus. The nucleus in the upper cell shows degenerative changes. Monkey 660 ♂. Hypophysectomized 45 days and treated with pregnant mare serum.  $\times 1300$ . Champy.  $4\mu$ . Severinghaus Altmann-Masson.

6 A dark oxyphil probably comparable to that shown in figure 9. The cytoplasm possesses an orange tinge and the central nucleus is degenerating. There is also a suggestion of cytoplasmic vesicles. Monkey 662 ♂.  $\times 1300$ . Champy.  $3\mu$ . Severinghaus Altmann-Masson.

7 A dark oxyphil with dark blue cytoplasmic background. The black bodies were a bright red in the preparation and are mitochondria. Filamentous mitochondria have accumulated in the portion of the pale principal cells bordering the capillary at the lower left. A U-shaped vesicle is visible to the right of the dark oxyphil. Monkey 662 ♂. Normal.  $\times 1300$ . Champy.  $3\mu$ . Severinghaus Altmann-Masson.

8 A pale oxyphil with large and irregularly-shaped mitochondria. A vacuole is present in the left portion of the cell. Monkey 662 ♂. Normal.  $\times 1300$ . Champy.  $3\mu$ . Severinghaus Altmann-Masson.

9 A dark oxyphil with homogeneous eosinophilic cytoplasm, vesicles and dark nucleus. This cell is probably degenerating. Monkey 658 ♂.  $\times 1300$ . Bouin.  $7\mu$ . Harris' hematoxylin and eosin.



## PLATE 2

### EXPLANATION OF FIGURES

10 Monkey 509 ♀. Control. 3.35 kg. The small black spots in the principal cells are juxtanuclear bodies. Thyroid and parathyroid are separated by an exceedingly small amount of connective tissue.  $\times 112$ . Bouin.  $4\mu$ . Harris' hematoxylin and eosin.

11 Monkey 634 ♀. Hypophysectomized 95 days. 3.5 kg. The darker cells at the left are the eosinophilic type which frequently occurred at the free surface of the gland. Note the absence of degeneration.  $\times 112$ . Bouin.  $4\mu$ . Harris' hematoxylin and eosin.

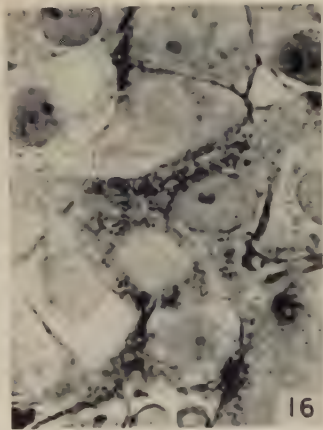
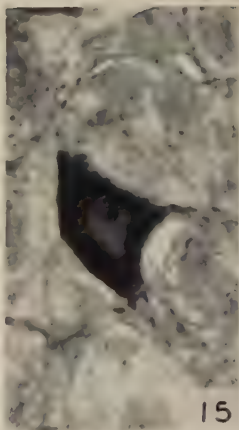
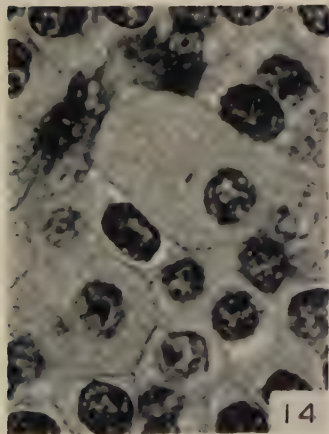
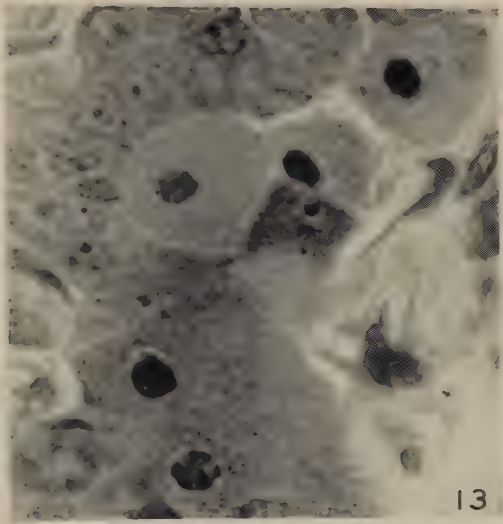
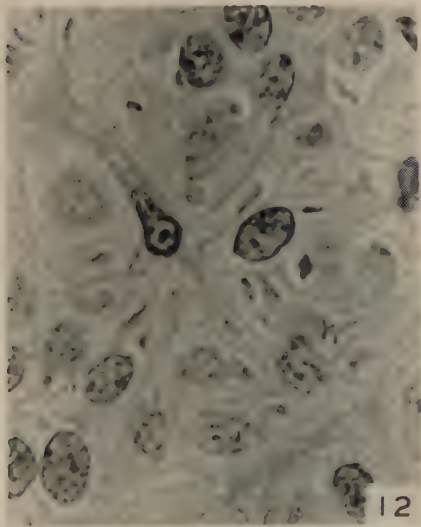
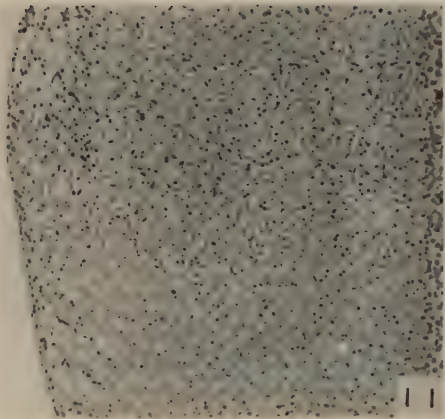
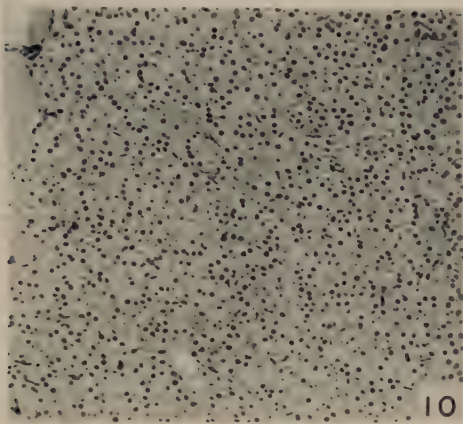
12 My 610 ♀. Treated with estradiol benzoate. The dark juxtanuclear bodies are shown in the cytoplasm of the principal cells.  $\times 1300$ . Bouin.  $4\mu$ . Harris' hematoxylin and eosin.

13 At the top are three pale oxyphils with granular cytoplasm and small dark nuclei. Bordered by the lower two of these cells is a small dark oxyphil with a nucleus not different from that of the principal cells. On the lower side are two large oxyphils intermediate in color and nuclear characteristics between the pale and dark oxyphils. Monkey 660 ♂. Hypophysectomized 45 days and pregnant mare serum-treated.  $\times 1300$ . Zenker-base.  $4\mu$ . Severinghaus Altmann-Masson.

14 Two oxyphils showing the granular cytoplasm which stains with either eosin or aniline blue. A dark structure which is probably a piece of the juxtanuclear body is visible in the largest oxyphil. Monkey 658 ♂.  $\times 1300$ . Bouin.  $7\mu$ . Harris' hematoxylin and eosin.

15 Dark oxyphil. The mitochondria are so dense that they appear to have coalesced. The nucleus is normal. An elliptical-shaped vesicle is present in a pale principal cell at the upper right. Monkey 660 ♂.  $\times 1300$ . Champy.  $4\mu$ . Severinghaus Altmann-Masson.

16 Two dark oxyphils with pale blue cytoplasm. These cells are closely related to the pale principal cells. Monkey 662 ♂. Normal.  $\times 1300$ . Champy.  $3\mu$ . Severinghaus Altmann-Masson.





## EFFECTS OF HYPOPHYSECTOMY AT MID-PREGNANCY IN THE MOUSE<sup>1</sup>

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TWO CHARTS AND THREE PLATES (THIRTEEN FIGURES)

Deficiencies of some endocrine glands seem to be alleviated during pregnancy or to become apparent only after parturition. An instance which might be cited is the failure of adrenal deficiency to appear in pregnant dogs (Rogoff and Stewart, '28; Swingle et al., '39). A comparatively large number of investigations concerned with the results of hypophysectomy during pregnancy have been reviewed (Smith, '39). Hypophysectomy of pregnant mice and rats, when performed during the latter part of the gestation period, usually did not affect the pregnancy except that labor was sometimes difficult and protracted, indicating that the birth mechanism may be impaired in some way (Selye et al., '33, '35). The (1) continued development of the mammary glands (Selye et al., '33; Newton and Beck, '39), (2) increase in body weight and (3) persistence of the corpora lutea of that pregnancy until the time of parturition have been the essential factors stressed in previous studies. The persistence of corpora lutea in hypophysectomized pregnant mice was not observed in one investigation (Selye et al., '33).

The present investigation was undertaken to study more extensively the influence of hypophysectomy during preg-

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nancy not only upon the factors mentioned above but also upon (1) maintenance of the ovarian stroma (2) the fate of follicles, especially those destined for ovulation on the day after parturition (in the normal animal), (3) the post partum mating reaction, and (4) the adrenal glands and kidneys. An attempt was also made to elucidate further the completeness with which the pregnant uterus or its contents (perhaps the placenta) may substitute for the endocrine function of the pituitary gland.

#### MATERIALS AND METHODS

Hybrid female mice approximately 3 months old were selected for these experiments. Twenty-nine females were placed with males and vaginal smears taken daily. The finding of vaginal plugs, or the presence of sperm in the smear, were taken as evidence of copulation for dating the onset of pregnancy. Of the above mice, twenty-four became pregnant following the first mating. Nineteen mice were hypophysectomized on the tenth day after copulation using the operative technique described by Thomas ('38). Body weights and vaginal smears were obtained at daily intervals until the end of the experiment. Five animals served as unoperated controls.

At about the time parturition was expected the pregnant animals were placed with active males to determine the possibility of post-parturitional copulation in the mice hypophysectomized at mid-pregnancy.

With few exceptions the operated and control mice were killed during the first or second day after the onset of labor or after completion of parturition. The mammary glands were removed on the skins and studied as "gross mounts" of stained and dissected preparations. The ovaries, uteri, vaginas and adrenals were fixed in Bouin's fluid and studied after sectioning and staining with hematoxylin and eosin. The adrenals and kidneys were dissected from the surrounding fatty connective tissue and weighed.

Serial sections of the pituitary region in the operated animals were examined microscopically for possible remaining hypophyseal tissue. Small fragments of hypophyseal tissue were detected in two operated mice (12 and 16, table 1). Since these fragments were minute and the animals failed to differ from the completely hypophysectomized mice, they have not been considered separately.

#### EFFECT OF HYPOPHYSECTOMY UPON THE COURSE AND DURATION OF PREGNANCY

Pregnancy terminated in three of the nineteen operated mice within 2 or 3 days following hypophysectomy, and one of these mice died on the fifth post-operative day (table 2, chart 2). The termination of pregnancy was indicated by progressive loss in weight and the presence of excessive blood in the vaginal smear. Pregnancy terminated on the twelfth day in one unoperated control. Sixteen hypophysectomized and four unoperated mice carried litters to term.

Difficult and prolonged parturition was observed in seven of the sixteen operated mice (table 1). Two of these mice died with living young in utero and two others were sacrificed with dead young in utero. With one exception parturition started in all of the operated mice on the twentieth to twenty-first days after observation of the vaginal plugs and 10 or 11 days after hypophysectomy. The other nine operated mice successfully delivered litters. The litters of three unoperated controls were delivered 20 days after insemination, and one after 19 days.

#### MATING REACTIONS AFTER HYPOPHYSECTOMY AT MID-PREGNANCY AND PARTURITION AT FULL TERM

The four control mice mated during the first day after parturition. This was determined either by finding vaginal plugs in the living mouse, sperm in the vaginal smear, or identification of sperm in the vagina after sectioning. Also fertilized eggs were found in the uterine tubes of the control animals.

With one exception, there was no evidence of mating in the operated animals. The exceptional mouse which had a vaginal plug, had delivered several embryos, two were still in utero and one dead embryo was still in the cervix and vagina. This may have been a case of "dominant male."

TABLE 1

*Data concerning gestation, parturition and mammary development and secretion.*

| NUMBER OF<br>MOUSE | DAYS POST<br>MATING AT<br>PARTURITION | DAYS POST<br>OPERATIVE AT<br>PARTURITION | DAYS POST<br>PARTUM<br>WHEN KILLED | NATURE OF<br>PARTURITION | MAMMARY<br>GLANDS: GROWTH<br>AND SECRETION |
|--------------------|---------------------------------------|------------------------------------------|------------------------------------|--------------------------|--------------------------------------------|
| Operated           |                                       |                                          |                                    |                          |                                            |
| 1                  | 20                                    | 10                                       | 1                                  | Normal                   | 4                                          |
| 2                  | 21                                    | 11                                       | 1                                  | Incomplete               | 2                                          |
| 3                  | 20                                    | 10                                       | 2                                  | Normal                   | 1                                          |
| 7                  | 23                                    | 12                                       | 2                                  | 2nd day                  | 2                                          |
| 11                 | 20                                    | 10                                       | 2                                  | Normal                   | 2                                          |
| 12                 | 21                                    | 11                                       | 1                                  | Normal                   | 2+                                         |
| 13                 | 20                                    | 10                                       | 2                                  | Normal                   | 2                                          |
| 15                 | 20                                    | 10                                       | 1                                  | Normal                   | 2+                                         |
| 16                 | 20                                    | 10                                       | 2                                  | Normal                   | 1                                          |
| 17                 | 20                                    | 10                                       | 2                                  | 2nd day<br>Incomplete    | 2+                                         |
| 18                 | 21                                    | 11                                       | 2                                  | 3rd day<br>Incomplete    | 1                                          |
| 19                 | 21                                    | 11                                       | 1                                  | Normal                   | 4                                          |
| 22                 | 20                                    | 10                                       | 2                                  | 2nd day<br>Incomplete    | 3                                          |
| 24                 | 21                                    | 11                                       | 0                                  | Not started              | 3                                          |
| 25                 | 20                                    | 10                                       | 2                                  | 2nd day<br>Incomplete    | 3                                          |
| 29                 | 20                                    | 10                                       | 2                                  | Normal                   | 1                                          |
| Controls           |                                       |                                          |                                    |                          |                                            |
| 4                  | 20                                    |                                          | 1                                  | Normal                   | 4                                          |
| 14                 | 19                                    |                                          | 2                                  | Normal                   | 4                                          |
| 20                 | 20                                    |                                          | 1                                  | Normal                   | 2                                          |
| 23                 | 20                                    |                                          | 2                                  | Normal                   | 4                                          |

*Body weights.* The body weights of the pregnant mice began to increase from the sixth to the eighth day after mating. The average increase exceeded the initial weights by about 1.5 gm. by the tenth day (charts 1 and 2; table 2). The operated mice lost 1 to 2 gm. on the first post-operative day, but quickly

recovered so that their weight curves paralleled those of the unoperated mice. The weight increment was correlated with the number of fetuses developing, as far as could be determined. In several litters the exact number of young born could not be ascertained. Hypophysectomy did not alter the weight increment appreciably following the rapid recovery from the operation.

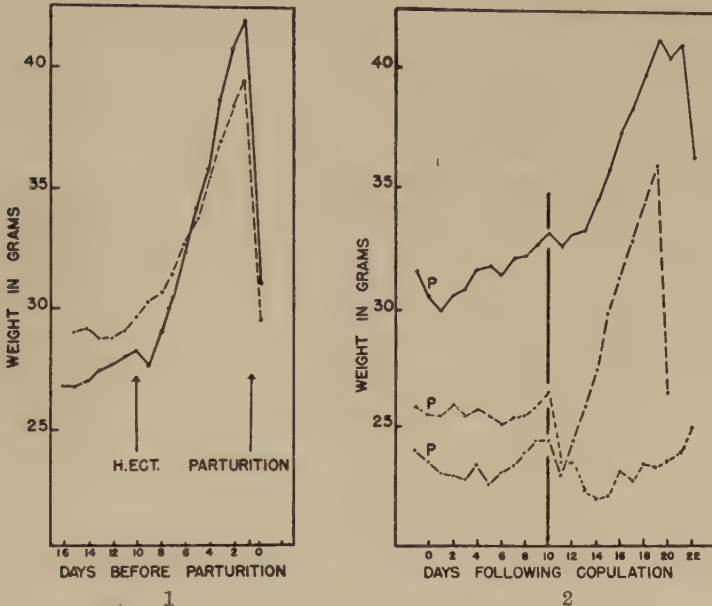


Chart 1 The average of the daily weights of sixteen hypophysectomized pregnant mice (solid line) and four unoperated controls (broken line). H.Ect. — time of operation.

Chart 2 The daily weight curves of two mice hypophysectomized on the tenth day of pregnancy (mouse 7, solid line and 15, dot and dash) and an operated mouse 9, (broken line) in which pregnancy was not completed.

*Adrenals.* The adrenal glands of the unoperated mice weighed from 5.75 to 7.5 mg. (average 6.9 mg.) when obtained on the first and second days after parturition. The adrenals of the operated mice at the end of gestation weighed from 2.5 to 5 mg. (average 3.8 mg.), therefore uniformly smaller and more atrophic than those of the controls (table 2).

Histological study showed in the unoperated animals a typical normal adrenal cortex (figs. 1 and 4). The fascicular and perimedullary zones made up most of the cortex. The fascicular cells were large, and had distinct cell membranes and pale cytoplasm. The perimedullary zone was thickened by accumulation of tissue, apparently undergoing fatty degeneration. The adrenal glands of one control mouse in which abortion occurred on the twelfth day resembled those of the other unoperated controls.

TABLE 2

*Weights of animals and organs and length of interpubic ligaments.*

| GROUP    | NUMBER OF MOUSE | WEIGHT AT 10TH DAY OF PREGNANCY | WEIGHT AT PARTURITION | WEIGHT AT DEATH | ADRENAL WEIGHTS  | RENAL WEIGHTS | RENAL WEIGHT/BODY WEIGHT | LENGTH OF INTER-PUBIC LIGAMENT |
|----------|-----------------|---------------------------------|-----------------------|-----------------|------------------|---------------|--------------------------|--------------------------------|
|          |                 | <i>gm.</i>                      | <i>gm.</i>            | <i>gm.</i>      | <i>mg.</i>       | <i>mg.</i>    |                          | <i>mm.</i>                     |
| Operated | 1               | 27.3                            | 39.4                  | 27.8            | 3.75             | 377           | 13.8                     | 2.25                           |
|          | 2               | 27                              | 43.9                  | 29              | 4                | 372.8         | 13.8                     | 4.5                            |
|          | 3               | 26.9                            | 44.1                  | 27.4            | 3.25             | 313           | 11.6                     | 2                              |
|          | 7               | 33.1                            | 41                    | 36.2            | 4                | 331           | 10                       | 5                              |
|          | 11              | 31.4                            | 38.9                  | 28.5            | 4.5              | 360           | 11.4                     | 2                              |
|          | 12              | 31.2                            | 48.9                  | 31.9            | 3.7              | 408           | 12.7                     | 2.5                            |
|          | 13              | 27.6                            | 37.6                  | 24.4            | 5                | 301           | 10.9                     | 1.75                           |
|          | 15              | 24.4                            | 35.7                  | 26.5            | 3                | 316           | 12.9                     | 2.5                            |
|          | 16              | 26                              | 34.5                  | 25.9            | 3.75             | 339           | 13                       | 1                              |
|          | 17              | 27.4                            | 41.6                  | 38.4            | 3.5              | 370           | 13.5                     | 5                              |
|          | 18              | 27.9                            | 40                    | 28.3            | 4.5              | 313           | 11.2                     | 4                              |
|          | 19              | 27.9                            | 45                    | 27.1            | 2.5              | 358           | 12.8                     | 4.5                            |
|          | 22              | 31                              | 45                    | 30.8            | 4                | 360           | 11.6                     | 2                              |
|          | 24              | 27.5                            | 43.5                  | 42              | 3.25             | 338           | 12.3                     | 3.75                           |
|          | 25              | 30                              | 49                    | 28.2            | 5                | 337           | 11.2                     | 4.5                            |
|          | 29              | 28                              | 41.7                  | 25.8            | 4                | 394           | 13.7                     | 1                              |
|          | Average         | 28.2                            | 41.8                  | 30.9            |                  |               | 12.3                     |                                |
| Control  | 4               | 28.8                            | 40                    | 29.2            | 7                | 416           | 14.1                     | 2.5                            |
|          | 14              | 28.6                            | 40.6                  | 29              | 5.75             | 379           | 13.2                     | 2                              |
|          | 20              | 32.6                            | 43.9                  | 33.7            | 7.5              | 468           | 14.3                     | 2.5                            |
|          | 23              | 28.5                            | 33.5                  | 27.8            | 7.5              | 461           | 16.4                     | 1.5                            |
|          | Average         | 29.6                            | 39.5                  | 29.7            |                  |               | 14.5                     |                                |
| Aborted  | 9               | 26.5                            | ....                  | 25.1            | 3.5              | 245           | 9.2                      | <1                             |
|          | 28              | 27.4                            | ....                  | 21.5            | 3                | 273           | 9.9                      | 0                              |
|          | 8 <sup>1</sup>  | 27.5                            | ....                  | 23.7            | 7.3 <sup>1</sup> | 369           | 13.4                     | 0                              |

<sup>1</sup> Unoperated.

In the hypophysectomized mice the fascicular zones of the adrenal glands were greatly reduced in thickness (figs. 2, 3 and 5). The individual cells had decreased in size and also the columns contained fewer cells. The glomerular zone was irregular, in some places extending into the fascicular zone. The reticular or perimedullar zone contained areas of cells showing fatty degeneration, or areas in which the cells were lacking, only vascular sinuses persisting. Both of the two conditions occasionally existed at different areas in the same adrenal gland.

The adrenal glands of two mice which aborted following hypophysectomy weighed 3 and 3.5 mg. respectively. Histologically these glands resembled those of the pregnant operated mice (fig. 2).

The pregnant uterus and its contents was apparently undisturbed by the adrenal regression during the latter half of pregnancy. Also, the evidence clearly indicates that the pregnant uterus and its contents were not capable of maintaining the adrenals in the absence of the hypophysis.

*The ovaries, during or following parturition.* In the four unoperated control animals, ovulation had occurred on the day after parturition, because fertilized eggs were found in the tubes and recent corpora lutea in the ovaries. Two control mice had eggs at various stages of formation of the second maturation spindle located in proximal loops of the tube, in a third mouse male and female pronuclei were present. In the fourth control, the tubal eggs were in the 2-cell stage. This last animal had been killed on the second day post partum.

In the first three mice the most recent corpora lutea, corresponding to eggs in the tube, were still collapsed. They showed little ingrowth of vascular tissues or cells from the theca. Ovulation points had not healed over and the corpora had not been redistended. The luteal cells still retained most of their follicular characteristics (fig. 6). The corpora of the other animal, corresponding to the tubal eggs in the 2-cell stage, had been partly redistended as indicated by "tertiary

liquor folliculi" in the centers and were in a later state of development.

The operated animals showed no signs of recent ovulation. The loops of the tubes were collapsed, instead of several being filled with secretion, as is the case when tubal eggs are present. There were no recent corpora lutea, the only ones recognizable being the corpora of the past pregnancy.

These corpora of the last pregnancy looked quite normal (fig. 8). It was evident that the corpora lutea of the operated pregnant mice were as well preserved as those of the pregnant controls (fig. 8). The luteal cells showed no signs of vacuolation, such as described by Pfeiffer ('41) in the corpora lutea of his "constant-estrus" animals, which had ovulated and become pregnant after injections of luteinizing hormone.

*The follicles which might have ovulated.* The follicles destined for post partum ovulation, if the animals had not been hypophysectomized, were easily identified (fig. 7). They had three to six layers of follicle cells, but only small amounts of liquor folliculi. The ova of these follicles contained first maturation spindles. Some contained first polar bodies, others did not. Mitoses were often present although not numerous in the granulosa cells, but very rare in the theca of these atretic follicles. Division of granulosa cells in these follicles was considered an indication that atresia was only just beginning. Sometimes pycnotic or hyperchromatic follicle cells closely surrounded the ovum. Counts of these follicles showed a number corresponding with the number usually ovulated (table 3, column 7). Also present were a few follicles in early atresia with nuclei of the ova still intact.

It is evident that these follicles had attained a medium stage of development before parturition. Further development of the follicles was apparently interrupted. They failed to undergo preovulatory distention and ovulation. The ova in these follicles either completed the formation of the first maturation spindle and gave off the first polar body or at least formed the first polar spindle. This would indicate that

maturation changes in these ova do not depend upon a gonadotrophic secretion from the pituitary.

The medium sized follicles in these ovaries seemed to be growing quite normally as indicated by the high incidence of mitotic figures in the granulosa cells. There was no evidence that ovarian follicles of the hypophysectomized mice, operated

TABLE 3

*Ovaries of mice hypophysectomized at mid-pregnancy and killed toward the end of gestation or just after parturition.*

| MICE     | STAGE<br>AT<br>DEATH <sup>1</sup> | HOURS<br>POST<br>PARTUM | OVULA-<br>TION | RECENT<br>CL AND<br>TUBAL<br>OVA | C.L.O.F<br>(PAST<br>PREG-<br>NANCY | FOLLICLES <sup>2</sup> |        |                  |
|----------|-----------------------------------|-------------------------|----------------|----------------------------------|------------------------------------|------------------------|--------|------------------|
|          |                                   |                         |                |                                  |                                    | Early atresia          |        | Normal<br>medium |
|          |                                   |                         |                |                                  |                                    | Spindles               | Nuclei |                  |
| Operated |                                   |                         |                |                                  |                                    |                        |        |                  |
| 1        | 3                                 | <17                     | —              | 0                                | 2                                  | 8                      | 5      | 7                |
| 2        | 2                                 | —                       | —              | 0                                | 7                                  | 16                     | 7      | 16               |
| 3        | 3-4                               | >22                     | —              | 0                                | 5                                  | 11                     | 2      | 13               |
| 7        | 2                                 | —                       | —              | 0                                | 6                                  | 7                      | 3      | 6                |
| 11       | 4                                 | >26                     | —              | 0                                | 4                                  | 5                      | 0      | 11               |
| 12       | 3                                 | > 4, <23                | —              | 0                                | 6                                  | 5                      | 1      | 2                |
| 13       | 3-4                               | >22                     | —              | 0                                | 4                                  | 7                      | 3      | 8                |
| 15       | 3                                 | > 7½                    | —              | 0                                | 4                                  | 3                      | 0      | 4                |
| 16       | 4                                 | >26                     | —              | 0                                | 4                                  | 12                     | 2      | 12               |
| 17       | 2                                 | —                       | —              | 0                                | 4                                  | 2                      | 0      | 2                |
| 18       | 2                                 | —                       | —              | 0                                | 3                                  | 6                      | 3      | 7                |
| 19       | 3                                 | > 5                     | —              | 0                                | 5                                  | 15                     | 4      | 8                |
| 22       | 2                                 | —                       | —              | 0                                | 6                                  | 3                      | 7      | 7                |
| 24       | 1                                 | —                       | —              | 0                                | 7                                  | 6                      | 2      | 8                |
| 25       | 3                                 | —                       | —              | 0                                | 7                                  | 8                      | 1      | 6                |
| 29       | 3                                 | >30                     | —              | 0                                | 6                                  | 2                      | 3      | 9                |
| Controls |                                   |                         |                |                                  |                                    |                        |        |                  |
| 4        | 3                                 | >19                     | +              | 4                                | 7                                  | 2                      | 0      | 17               |
| 14       | 3                                 | >26                     | +              | 5                                | 7                                  | 1                      | 0      | 14               |
| 20       | 3                                 | >20                     | +              | 7                                | 6                                  | 5                      | 6      | 11               |
| 23       | 4                                 | >27                     | +              | 5                                | 5                                  | 9                      | 3      | 10               |

<sup>1</sup> Stage at death:

- 1 — Toward end of gestation, before onset of labor.
- 2 — During difficult or protracted labor.
- 3 — The day after parturition.
- 4 — Early the second day after parturition.

<sup>2</sup> In one ovary only.

during mid-pregnancy, develop further than those of hypophysectomized non-pregnant animals.

Study of the germinal epithelium of the control ovaries showed evidence of proliferation; incidence of mitoses was fairly high, especially in the animal which had ovulated on the second day before death. These mitoses might contribute either to repair of the ovulation points, to an increase in number of cells in the germinal epithelium, or to genesis of new ova.

The germinal epithelium of the ovaries of the operated animals was quite different. In the first place it had been noted at autopsy that the ovaries were much smaller and less vascular. The cells of the germinal epithelium were closely crowded together, sometimes almost pseudo-stratified. The surface of the ovary was wrinkled in some places. Nuclei of the cells were hypochromatic. It was difficult to identify mitotic figures in the germinal epithelium of these ovaries.

*Ovarian stroma.* The relative amounts of ovarian stroma, as compared with follicular or luteal tissue, were similar in the ovaries of both operated and unoperated animals. The ovarian stroma of the operated animals showed characteristic qualitative differences from that of the controls (figs. 7 and 8). The relative density of the chromatic nuclei was significantly greater in the operated animals. Also the number of nuclei per unit area were apparently increased and the cytoplasmic and intercellular substance decreased. The ovarian stroma of the operated mice was thus composed of a highly cellular tissue with densely staining nuclei. In the unoperated animals the nuclei were more vesicular, larger and separated by relatively greater amounts of cytoplasmic and intercellular substance.

In animals of both groups large yellowish or brownish cells were found scattered throughout the stroma. The number of these pigmented cells, possibly macrophages, was definitely greater in the ovaries of the operated animals.

*Mammary glands.* The mammary glands of three of the unoperated control mice were thickened and whitish when

removed on the first or second days after parturition. The glands of the fourth mouse were thinner, pink, and the ducts were filled with white fluid. Sections and whole mounts of the glands revealed extensive lactation in the three mice. The alveoli were distended. The alveolar epithelium was still cuboidal and contained vacuoles. The mammary alveoli of the fourth mouse were slightly distended and the epithelial cells were apparently just beginning active secretion.

The glands of two of the operated mice killed in less than 24 hours after parturition likewise showed well developed lactation. The glands were thick and white at the time they were removed. The alveoli and ducts were greatly distended with milk (rated 4 in table 1, figs. 10 and 13). In four of the seven mice killed during the second day post partum, the mammary glands were only moderately thickened and, although fully developed, showed little evidence of secretory activity. The ducts and alveoli contained little or no secretion, and the epithelium showed little evidence of lactation (rated 1 in table 1; figs. 11 and 12). The mammary glands of the other mice showed intermediate stages of secretory activity (table 1). With few exceptions the glands on the second day post partum were more poorly developed than those of mice removed within 24 hours of parturition.

*Kidneys.* The weights of the kidneys of the hypophysectomized pregnant and control mice were compared on the basis of body weight using the body weights obtained at the tenth day of pregnancy. The relative renal weights were thus determined as milligrams of kidney per gram of body. The means of the ratios were 12.3 and 14.5 for the operated and control mice respectively and 9.5 and 13.4 for the operated and control mice in which pregnancy did not continue to term. The mean renal weight to body weight ratios were 12.6 and 11.9 for the operated mice killed on the first and second day post partum respectively.

*The uteri.* One of the most prominent features of the uteri of both control and operated animals was the folding of the longitudinal muscles, probably due to the strong contraction

of the inner circular layer. The uterine mucosa was frequently heavily infiltrated with leukocytes and the cells of the epithelium were vacuolated. The uterine stroma often contained large tissue spaces, perhaps indicative of the extensive trauma incident to parturition.

One clear difference between the control and operated animals was the evidence of some secretion of uterine epithelium of the normal animals (in one case there was considerable cystic hyperplasia of the endometrium). This is probably an aftermath of the post parturitional estrus in these animals during which ovulation had recently occurred. It was absent from the operated animals.

*The vagina.* Animals sacrificed toward the end of gestation, or during a difficult and protracted labor, showed the external mucous layers of the vagina still intact, as is typical of late pregnancy. In the control animals which had completed delivery and mated, it was very difficult to recognize mucous cells, although they had undoubtedly been present within a day of the time of death. In some cases a cornified layer appeared under the mucous layers in animals in which parturition had been recent. On the second day post partum, in the normal control in which 2-celled eggs were present in the tubes, the vagina was extensively infiltrated with leukocytes.

#### DISCUSSION

The well-known regulation of gonadal function by the hypophysis must be altered during pregnancy, or at least it is capable of alteration. Ovariectomy is incompatible with the progress of pregnancy in some species of animals, although in these same species, the removal of the hypophysis does not alter the course of gestation. The embryos not only grow progressively but the mammary glands develop and in the mouse the pubic rami are partly resorbed and the symphysis replaced by an interpubic ligament as occurs in intact pregnant mice (Gardner, '36). Both the mammary and pelvic changes occurred in hypophysectomized mice with intact placentas after destruction of the embryos (Newton and Beck, '39). The

progressive increase in weight of hypophysectomized pregnant mice indicates that their metabolic needs must correspond to those of an unoperated animal. A portion of the weight increment of pregnant mice is not related directly to the growth of the embryos but to a maternal retention of water. Hypophysectomized mice with intact placentas showed less loss of weight than those without placentas, and it was concluded that the retained placenta maintained the positive water balance (Newton and Beck, '39).

The uteri of mice pregnant 10 days or more do not require internal secretory support from the hypophysis. At the same time they seem to provoke changes in the mammary glands and pelvis. The reactions apparently depend upon the placentas which in turn depend upon intact ovaries and, for reasons stated above, not on the fetal hypophyses.

The pregnant uterus and its contents did not however completely compensate for hypophyseal function. The adrenal glands regressed as rapidly as they did following hypophysectomy in non-pregnant animals. The kidneys lost some weight during the last half of gestation, and more following parturition. Although the corpora lutea were maintained in both the pregnant hypophysectomized and intact mice, the ovarian interstitial tissue regressed in the hypophysectomized pregnant mice. The medium sized follicles did not complete the late stages of their development as usually occurs following parturition in mice. Distention with liquor folliculi and ovulation did not occur. However, the ova destined in the unoperated animal for post partum ovulation undergo early maturation stages to the formation of the first spindle, and in some cases, the first polar body, the stage reached normally at ovulation. This would be compatible with changes observed in ova explanted from the follicles, which, when removed to tissue cultures went through maturation stages without pituitary stimulation (Pincus, '36).

The above changes therefore might be summarized by stating that during pregnancy and in the absence of the hypophysis principles are present maintaining the corpora lutea (leuto-

trophic) the development and early secretion of the mammary glands (mammogenic and lactogenic) and the capacity for the increase in body weight (growth factor). The regression of the interstitial tissue of the ovaries and adrenal cortex indicates a deficiency of other factors (interstitial-cell-stimulating and adrenotrophic) in the pregnant and hypophysectomized animals. The failure of preovulatory enlargement and post parturitional ovulation of the follicles which would have ovulated otherwise indicates again their dependence upon pituitary stimulation (gonadotropic). The recognition of these follicles in early stages of atresia but with their ova in early maturation stages, indicates the independence of these phenomena of maturation from pituitary regulation.

The necessity of active corpora lutea for the maintenance of gestation has been demonstrated in rats and mice by the termination of pregnancy following ovariectomy (see Allen et al., '39) and in rats with experimentally altered ovarian function (Pfeiffer, '41). These deficiencies may be compensated in some species by injections of progestion (Allen and Corner, '29) or pituitary leutinizing hormone respectively. Recently prolactin has been found to maintain functional corpora lutea in hypophysectomized rats, as determined by the decidual response of the traumatized uterus (Evans et al., '41).

The mammary glands of hypophysectomized male mice developed when estrogen was administered together with either progesterone or prolactin (Gardner, '41; Gardner and White, '41). The factors responsible for the maintenance of the corpora lutea and development of the mammary glands of hypophysectomized pregnant mice therefore may be the same or be closely related.

The regressive changes in the adrenal glands during pregnancy are of considerable interest. The regression was as rapid as in non-pregnant mice. The adrenal glands of some species are apparently less essential during pregnancy than in non-pregnant animals (Rogoff and Stewart, '28; Swingle et al., '37). Progesterone may be active in compensating for

the vital deficiency created by adrenalectomy (Gaunt and Hays, '38). The numerous papers relating to the regression of the x-zone and hypertrophy of the adrenals of mice during normal gestation cannot be discussed here.

The deficiencies of the adrenals must be compensated by injections of salt or adrenocorticotropic material in order to maintain lactation in hypophysectomized rats or guinea pigs receiving comparatively purified lactogenic hormone (Gaunt and Tobin, '36; Nelson and Gaunt, '36 and '37; Gomez and Turner, '36). The onset of lactation occurred in the hypophysectomized, pregnant mice although the adrenal glands were regressing. The present experiments do not clarify the factors responsible for onset of lactation; whether the atrophic adrenal glands, the fetal adrenal glands or some substance otherwise associated with pregnancy. The crop-gland stimulating substance obtained by an isoelectric preparation of an adrenal extract (Spoor et al., '41) cannot be considered as an essential factor for the onset of lactation unless the atrophic adrenal glands contain a large amount of such a substance or unless the fetal adrenal glands are active.

#### SUMMARY

1. Mice hypophysectomized at mid-pregnancy recover quickly, increase in weight as do unoperated pregnant mice, and the majority deliver normal litters at the expected time. A minority, usually primipara, may have difficult or protracted labor.

2. The corpora lutea of pregnancy in the operated animals compare favorably with those of normal mice at the end of gestation, indicating the presence of a luteotrophin or that a pituitary luteotrophin is not essential.

3. The adrenal glands undergo a marked degree of cortical atrophy, but there are no signs of cortical deficiency while pregnancy continues. Perhaps secretion of progesterone compensates. There is no evidence of placental compensation for pituitary adrenotrophin.

4. The ova in the follicles which would have ovulated after parturition, if the mice had not been hypophysectomized, undergo early maturation stages; the formation of the first polar spindle and sometimes the first polar body. There is little secretion of liquor folliculi or other preovulatory change in these atretic follicles.

5. Retrogression of ovarian interstitial tissue indicates absence of interstitial-cell-stimulating function in the hypophysectomized pregnant mice.

6. Continued development of the mammary glands and onset of lactation in all of the operated mice killed during the day following parturition indicates a compensatory source of mammotrophic and lactogenic secretion during the latter half of pregnancy in the absence of the hypophysis.

7. Resorption of medial ends of pubic rami and replacement of the symphysis pubis by an interpubic ligament proceeds as well in the operated as in the control animals.

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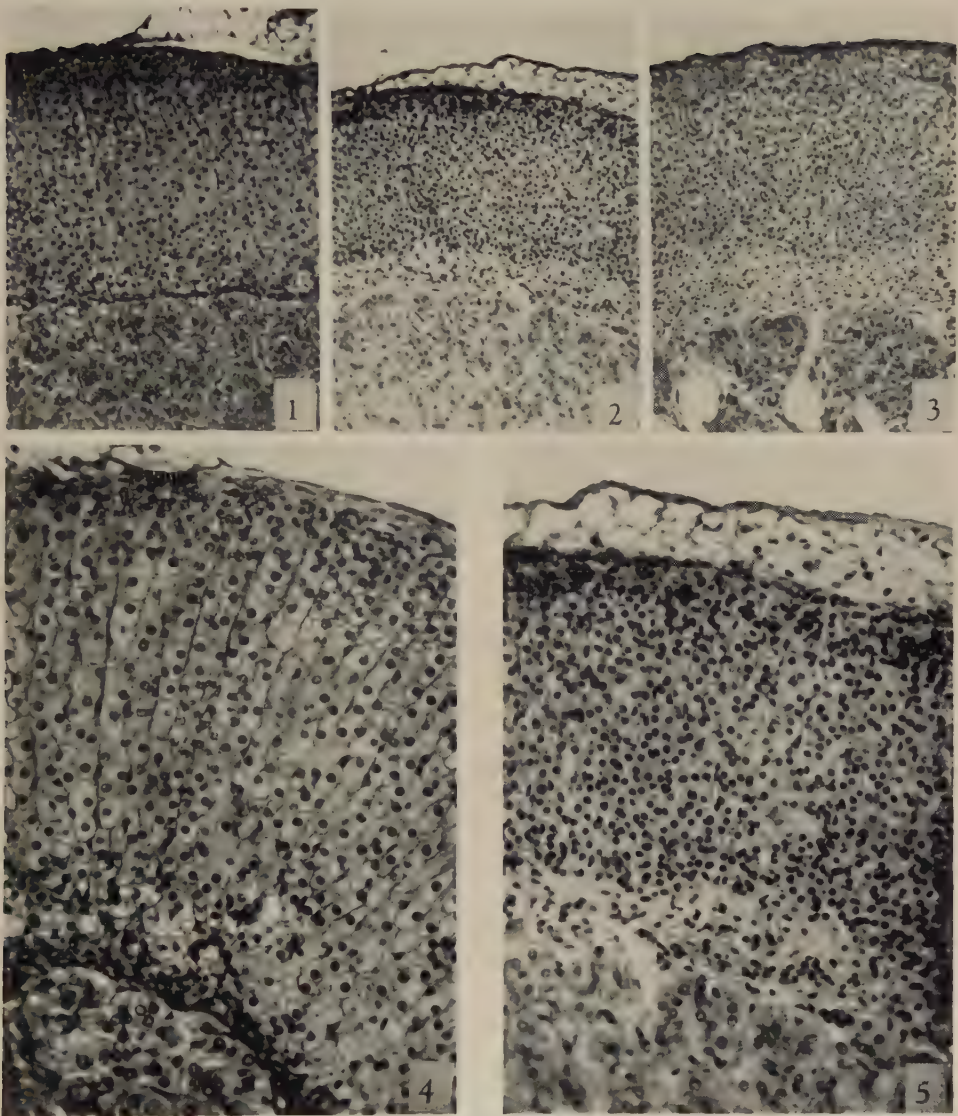
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## PLATE 1

### EXPLANATION OF FIGURES

1, 2 and 3 Photomicrographs of sections of the adrenal cortices,  $\times 85$ ; (1) from an unoperated control (20) killed within 24 hours of parturition, adrenal weight 7.5 mg.; (2) from a hypophysectomized mouse aborting after operation at mid-pregnancy and killed 22 days after insemination, adrenal weight 3.0 mg., and (3) from mouse 17 killed within 12 hours of parturition, adrenal weight 3.5 mg.

4 and 5 Photomicrographs of sections of adrenal cortices ( $\times 170$ ). Same adrenals shown in figures 1 and 2 above respectively.

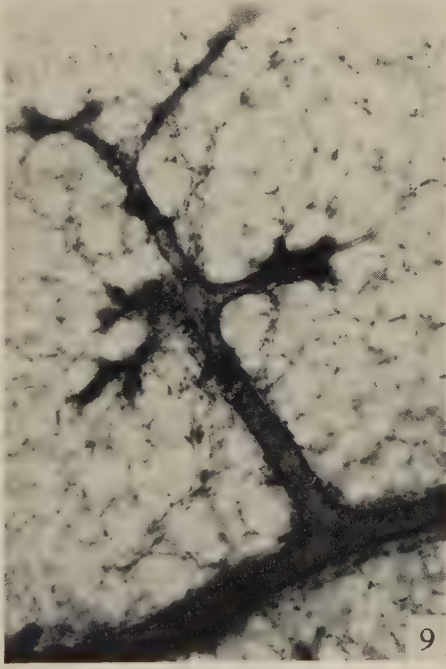
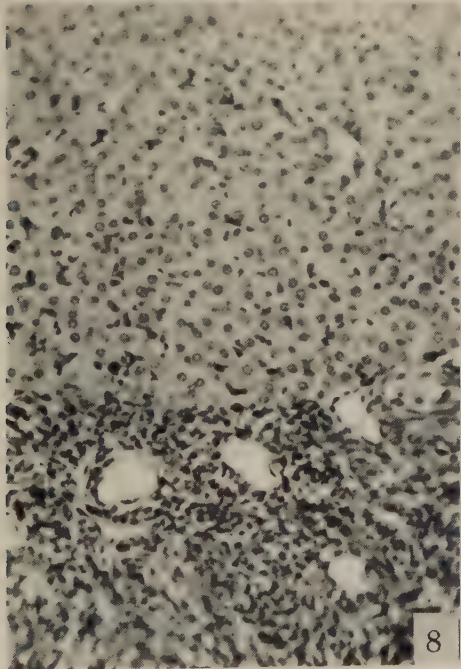
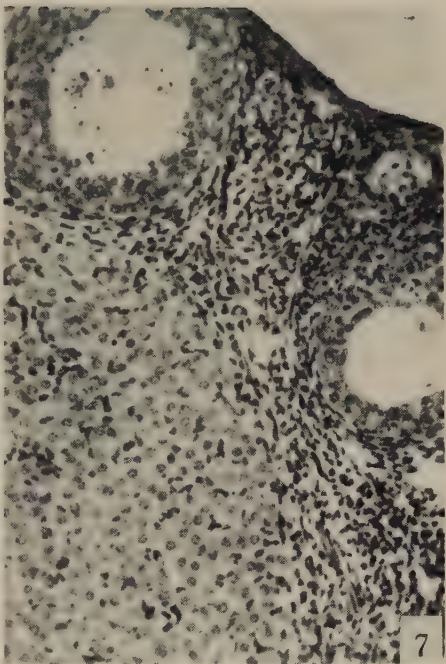
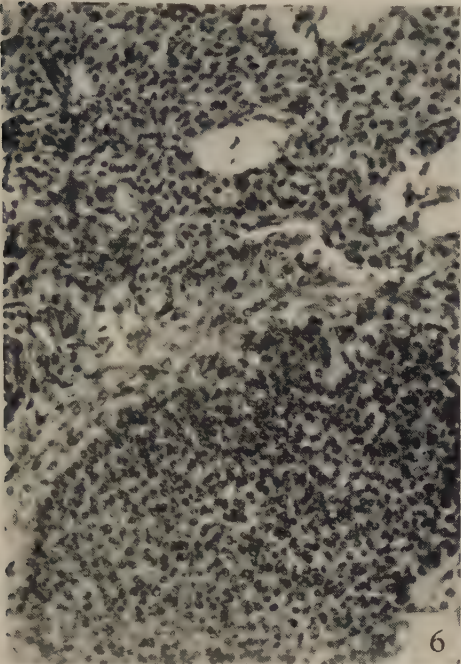


## PLATE 2

### EXPLANATION OF FIGURES

6, 7 and 8 Photomicrographs of sections of ovaries with corpora lutea,  $\times 170$ ; (fig. 6) from an unoperated control mouse (23) showing a recent corpus luteum (lower right) and normal stroma; (fig. 7) from a hypophysectomized mouse (11) killed on the second day post partum and showing dense stroma, a well-developed corpus luteum and atretic follicles; and (fig. 8) from an unoperated mouse (23) showing a corpus luteum of the pregnancy which ended on the second day before death. Compare corpus luteum with that of operated animal in figure 7.

9 A photomicrograph of a section of one of the stained and dissected mammary glands from a mouse (9) which aborted following hypophysectomy on the tenth day of pregnancy and was killed 22 days after mating.  $\times 85$ . The gland consisted of atrophic ducts in a fatty stroma.



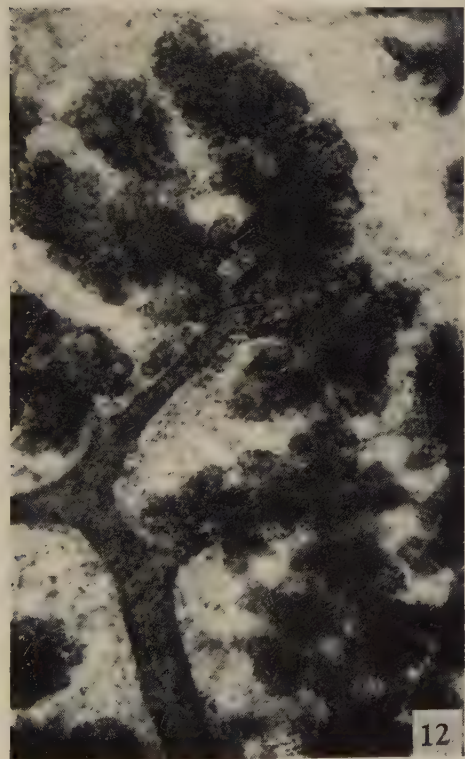
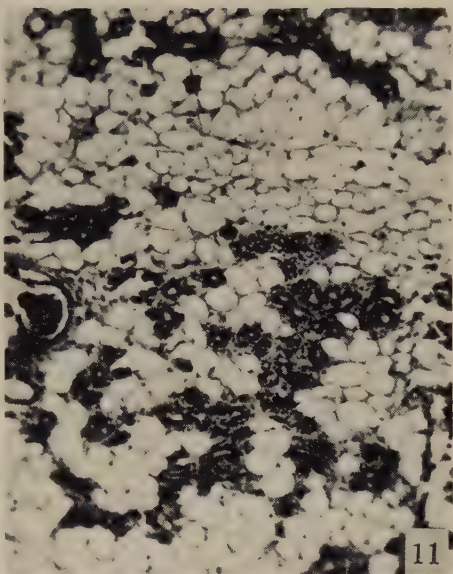
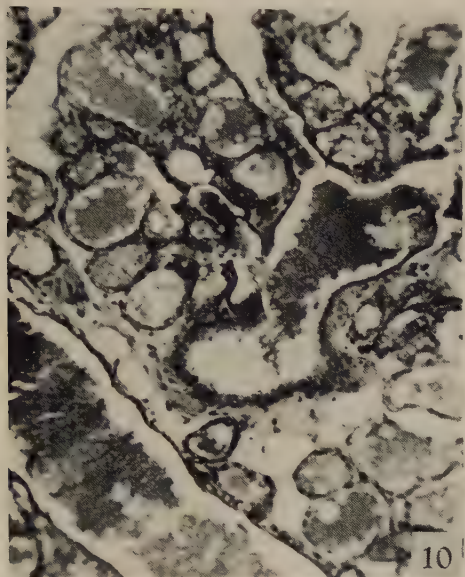
### PLATE 3

#### EXPLANATION OF FIGURES

10 A section of mammary gland from a hypophysectomized mouse (19) killed during the first day after parturition. The mammary ducts and alveoli were well developed and distended with milk. Rated as type 4 in table 1.  $\times 85$ .

11 Mammary gland from a hypophysectomized mouse (29) which had delivered more than 30 hours and less than 48 hours prior to death. Mammary glands show little evidence of secretory activity. (Rated as 1 in table 1.)  $\times 85$ . Compare with figure 10 killed during the first day post partum.

12 and 13 Photographs of stained and dissected whole mounts of mammary glands of two mice hypophysectomized on the tenth day of pregnancy and killed on the second and first days post partum respectively. The mammary alveoli and ducts of mouse 16 (fig. 12) are largely empty. Compare with figure 11. Rated as type 1. The mammary ducts and alveoli of mouse 1 (fig. 13) are distended with secretion (type 4, table 1).





## CALCIFICATION AND OSSIFICATION

### THE FORMATION OF MEDULLARY BONE IN MALE AND CASTRATE PIGEONS UNDER THE INFLUENCE OF SEX HORMONES<sup>1</sup>

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FOUR FIGURES

We have previously reported that, while administration of estrogens to male pigeons in the spring leads to production of new bone in the medullary cavities of the long bones, it does not do so in the fall, and that castrated male pigeons do not develop bone after injection of the same dose of estradiol, in either spring or fall, that produced it in male pigeons in the spring (Bloom, Bloom, Domm and McLean, '40). This paper reports these experiments in detail, and brings additional evidence to the effect that androgen, as well as estrogen, is essential to the formation of medullary bone in pigeons.<sup>2</sup> A few experiments upon the administration of parathyroid extract to pigeons, in which medullary bone had been previously produced, are also reported.

The present experiments followed the investigations of Zondek ('37) on male chickens and of Pfeiffer and Gardner ('38 a) on male pigeons, by which it was shown that new bone developed in the marrow cavities of these birds as a result of injection of estrogens. Our experiments were undertaken

<sup>1</sup> This work was aided by grants from the Dr. Wallace C. and Clara A. Abbott Memorial Fund of the University of Chicago, and from the Josiah Macy, Jr., Foundation. We are indebted to Dr. Irwin Schwenk, of the Schering Corporation for supplying us, through the kindness of Dr. F. C. Koch, with the  $\alpha$ -estradiol and the testosterone propionate used in these experiments.

<sup>2</sup> A preliminary communication has been published: Bloom, M. A., W. Bloom and F. C. McLean, 1941, *Am. J. Physiol.*, vol. 133, p. P216.

with the idea that by stimulating bone formation through administration of estrogen, and by accelerating its destruction with parathyroid extract, we could obtain material suitable for studies of the cellular processes associated with bone formation and resorption. Much better material for these purposes having been found during the normal egg-laying cycles of pigeons (Bloom, Bloom and McLean, '41) and of chickens and ducks (Bloom, Bloom, Domm and McLean, '40), the present paper is concerned chiefly with the hormonal mediation of medullary bone formation and with other hormonal influences noted during the course of our experiments.

#### MATERIAL AND METHODS

The subjects of all the experiments reported were adult male pigeons, maintained under uniform laboratory conditions. Sixty of the ninety-two birds used were registered carrier pigeons from 1 to 2 years old. They received a mixed feed of corn, buckwheat, buckwheat cake, wheat, sunflower seed, oats, and an unlimited amount of crushed oyster shells and sand.

Detailed protocols of the experiments are included in the tables. The experiments were designed: to compare the differences in the response of intact and castrated males to  $\alpha$ -estradiol in the spring and in the fall or winter (table 1), to determine the effect of adding testosterone propionate, in varying doses, to a constant dose of  $\alpha$ -estradiol (table 2), to determine the minimum dose of  $\alpha$ -estradiol capable of producing medullary bone in castrate animals when testosterone propionate was also administered in optimum amounts (table 3), and to observe the effects of single doses of parathyroid extract, particularly upon medullary bone produced by the previous administration of  $\alpha$ -estradiol (table 4). In each case suitable controls were included. In these experiments we were concerned with the initial response to the agents administered, rather than with the end results of long-continued administration.

TABLE 1

*Comparison of endosteal reaction and formation of medullary bone in pigeon femurs, under influence of  $\alpha$ -estradiol, in the breeding and resting seasons. Testes were inspected or castration performed at laparotomy, usually 1 to 5 days before beginning of experimental period. Pigeons 8, 11 and 25 received approximately 80 gamma of  $\alpha$ -estradiol during a preliminary period of 32 days before large dosage specified in this table.*

| APRIL-JUNE |     |                     |      |                    | NOVEMBER-DECEMBER |        |                  |                     |      |                    |                |
|------------|-----|---------------------|------|--------------------|-------------------|--------|------------------|---------------------|------|--------------------|----------------|
| Pigeon     | Sex | $\alpha$ -estradiol | Time | Endosteal reaction | Medullary bone    | Pigeon | Sex              | $\alpha$ -estradiol | Time | Endosteal reaction | Medullary bone |
| No.        |     | $\gamma$ per day    | Days |                    |                   | No.    |                  | $\gamma$ per day    | Days |                    |                |
| 25         | M   | 66.5                | 14   | +                  | ++                | 40     | M                | 66.5                | 14   | +                  | 0              |
| 73         | M   | 66.5                | 14   | +                  | ++                | 52     | M                | 66.5                | 14   | Trace              | 0              |
| 77         | M   | 66.5                | 14   | +                  | ++                | 54     | M                | 66.5                | 15   | 0                  | 0              |
| 82         | M   | 66.5                | 14   | +                  | ++                | 55     | M                | 66.5                | 15   | 0                  | 0              |
| 85         | M   | 66.5                | 18   | +                  | ++                | 56     | M                | 66.5                | 13   | Trace              | 0              |
| 65         | M   | 66.5                | 21   | +                  | ++                | 57     | M                | 66.5                | 15   | 0                  | 0              |
| 67         | M   | 66.5                | 21   | +                  | ++                | 48     | $\frac{1}{2}$ C  | 66.5                | 15   | 0                  | 0              |
| 75         | M   | 66.5                | 21   | +                  | ++                | 39     | C <sup>max</sup> | 66.5                | 14   | Trace              | 0              |
| 79         | M   | 66.5                | 21   | +                  | ++                | 47     | C                | 66.5                | 15   | +                  | 0              |
| 61         | M   | 33.25               | 35   | +                  | ++                | 49     | C                | 66.5                | 15   | Little             | 0              |
| 63         | M   | 33.25               | 35   | +                  | +                 | 50     | C                | 66.5                | 15   | 0                  | 0              |
| 8          | C   | 66.5                | 14   | 0                  | 0                 | 51     | C                | 66.5                | 14   | Little             | 0              |
| 11         | C   | 66.5                | 10   | +                  | Trace             | 59     | C                | 66.5                | 14   | 0                  | 0              |
| 71         | M   | ....                | ..   | 0                  | 0                 | 60     | C                | 66.5                | 14   | 0                  | 0              |
| 81         | M   | ....                | ..   | 0                  | 0                 | 38     | M                | ....                | ..   | 0                  | 0              |
| 83         | M   | ....                | ..   | 0                  | 0                 | 42     | M                | ....                | ..   | 0                  | 0              |
| 84         | M   | ....                | ..   | 0                  | 0                 | 46     | M                | ....                | ..   | 0                  | 0              |
| 86         | M   | ....                | ..   | 0                  | 0                 | 89     | M                | ....                | ..   | 0                  | 0              |
|            |     |                     |      |                    |                   | 95     | M                | ....                | ..   | 0                  | 0              |

TABLE 2

*Effect of adding testosterone propionate, in varying doses, to a constant dose (66.5 gamma per day) of  $\alpha$ -estradiol. Experiment carried out in November-December, 1940. Testes inspected or castration performed at laparotomy 1 to 5 days before beginning of experimental period.*

| PIGEON | SEX | $\alpha$ -ESTRADIOL<br><br><i><math>\gamma</math> per day</i><br>..... | TESTOSTERONE<br>PROPIONATE<br><br><i>mg. per day</i><br>.... | TIME<br><br><i>Days</i><br>.. | SERUM CALCIUM                           |                                |                            | ENDOSTEAL<br>REACTION | MEDULLARY BONE |      |
|--------|-----|------------------------------------------------------------------------|--------------------------------------------------------------|-------------------------------|-----------------------------------------|--------------------------------|----------------------------|-----------------------|----------------|------|
|        |     |                                                                        |                                                              |                               | Individual<br><i>mM. per L.</i><br>2.24 | Average                        |                            |                       | mm.            |      |
|        |     |                                                                        |                                                              |                               |                                         | Sub-group<br><i>mM. per L.</i> | Group<br><i>mM. per L.</i> |                       |                |      |
| No.    |     |                                                                        |                                                              |                               |                                         |                                |                            |                       |                |      |
| 148    | M   | .....                                                                  | ....                                                         | ..                            | 2.24                                    |                                |                            | 0                     | 0              |      |
| 138    | C   | .....                                                                  | ....                                                         | ..                            | 2.15                                    |                                | 2.20                       | 0                     | 0              |      |
| 147    | M   | .....                                                                  | 1.0                                                          | 21                            | 2.44                                    |                                |                            | 0                     | 0              |      |
| 119    | C   | .....                                                                  | 1.0                                                          | 21                            | 2.64                                    |                                | 2.54                       | 0                     | 0              |      |
| 129    | M   | 66.5                                                                   | ...                                                          | 15                            | 3.91                                    |                                |                            | +                     | Trace          | 0.03 |
| 127    | M   | 66.5                                                                   | ...                                                          | 21                            | 2.63                                    |                                |                            | +                     | Trace          | 0.01 |
| 135    | M   | 66.5                                                                   | ...                                                          | 21                            | 3.80                                    | 3.44                           |                            | Trace                 | 0              |      |
| 120    | C   | 66.5                                                                   | ...                                                          | 16                            | 3.73                                    |                                |                            | 0                     | 0              |      |
| 109    | C   | 66.5                                                                   | ...                                                          | 21                            | 3.00                                    |                                |                            | 0                     | 0              |      |
| 123    | C   | 66.5                                                                   | ...                                                          | 21                            | 3.51                                    | 3.41                           | 3.43                       | +                     | Trace          | 0.01 |
| 134    | M   | 66.5                                                                   | 0.5                                                          | 14                            | 3.79                                    |                                |                            | +                     | +              | 0.2  |
| 130    | M   | 66.5                                                                   | 0.5                                                          | 21                            | 3.25                                    |                                |                            | +                     | +              | 0.1  |
| 144    | M   | 66.5                                                                   | 0.5                                                          | 21                            | 3.04                                    | 3.36                           |                            | +                     | +              | 0.1  |
| 107    | C   | 66.5                                                                   | 0.5                                                          | 14                            | 2.58                                    |                                |                            | +                     | +              | 0.1  |
| 106    | C   | 66.5                                                                   | 0.5                                                          | 21                            | 3.08                                    |                                |                            | +                     | +              | 0.25 |
| 118    | C   | 66.5                                                                   | 0.5                                                          | 21                            | 3.50                                    | 3.05                           | 3.21                       | +                     | +              | 0.4  |
| 131    | M   | 66.5                                                                   | 1.0                                                          | 14                            | 2.85                                    |                                |                            | +                     | +              | 0.35 |
| 108    | M   | 66.5                                                                   | 1.0                                                          | 21                            | 3.43                                    |                                |                            | +                     | +              | 0.3  |
| 145    | M   | 66.5                                                                   | 1.0                                                          | 21                            | 3.29                                    | 3.19                           |                            | +                     | +              | 0.25 |
| 114    | C   | 66.5                                                                   | 1.0                                                          | 14                            | 2.65                                    |                                |                            | +                     | +              | 0.1  |
| 116    | C   | 66.5                                                                   | 1.0                                                          | 21                            | 2.83                                    |                                |                            | +                     | +              | 0.65 |
| 136    | C   | 66.5                                                                   | 1.0                                                          | 21                            | 3.15                                    | 2.87                           | 3.03                       | +                     | +              | 0.25 |
| 133    | M   | 66.5                                                                   | 2.0                                                          | 14                            | 3.09                                    |                                |                            | +                     | +              | 0.1  |
| 132    | M   | 66.5                                                                   | 2.0                                                          | 21                            | 2.92                                    |                                |                            | +                     | +              | 0.55 |
| 146    | M   | 66.5                                                                   | 2.0                                                          | 21                            | 2.63                                    | 2.88                           |                            | +                     | +              | 0.45 |
| 141    | C   | 66.5                                                                   | 2.0                                                          | 14                            | 3.07                                    |                                |                            | +                     | +              | 0.45 |
| 110    | C   | 66.5                                                                   | 2.0                                                          | 21                            | 3.01                                    |                                |                            | +                     | +              | 0.25 |
| 115    | C   | 66.5                                                                   | 2.0                                                          | 21                            | 3.13                                    | 3.07                           | 2.98                       | +                     | +              | 0.3  |

At the beginning of each experiment laparotomies were performed upon all of the birds to be used, and the testes were removed or their size was noted. Crystalline  $\alpha$ -estradiol and testosterone propionate (Schering) were dissolved in sesame oil and injected into the breast muscles, as noted in the protocols of the experiments. At the ends of the experimental periods all pigeons were autopsied. The femur, sometimes

TABLE 3

*Effects of diminishing doses of  $\alpha$ -estradiol with a constant dose (1.0 mg. per day) of testosterone propionate. Experiment carried out in January–February, 1941. All animals castrated 1 to 5 days before experimental period, and sacrificed after 14 days of injections.*

| PIGEON | $\alpha$ -<br>ESTRADIOL | TESTOSTERONE<br>PROPIONATE | SERUM <sup>1</sup> |            | ENDOSTEAL<br>REACTION | MEDULLARY BONE |      |
|--------|-------------------------|----------------------------|--------------------|------------|-----------------------|----------------|------|
|        |                         |                            | Calcium            | Phosphate  |                       |                |      |
| No.    | $\gamma$ per day        | mg. per day                | mM. per L.         | mM. per L. |                       |                | mm.  |
| 179    | ....                    | ...                        | 2.45               |            | 0                     | 0              |      |
| 176    | ....                    | 1.0                        | 2.28               |            | 0                     | 0              |      |
| 171    | 50                      | ...                        | 2.49               | 0.59       | +                     | ++++           |      |
| 172    | 50                      | ...                        | 2.63               | 0.66       | ? + <sup>1</sup>      | 0              |      |
| 173    | 50                      | 1.0                        | 3.32               | 0.64       | +                     | +++            | 0.44 |
| 177    | 10                      | 1.0                        | 2.24               | 1.17       | +                     | ++             | 0.10 |
| 182    | 10                      | 1.0                        | 2.31               | 1.6        | +                     | ++             | 0.11 |
| 180    | 5                       | 1.0                        | 2.32               |            | +                     | ++             | 0.13 |
| 181    | 5                       | 1.0                        | 2.42               |            | +                     | +              | 0.04 |
| 174    | 2.5                     | 1.0                        | 2.70               |            | +                     | Trace          |      |
| 175    | 2.5                     | 1.0                        | 2.23               | 0.59       | +                     | Trace          |      |
| 169    | 1.0                     | 1.0                        | 2.15               | 0.86       | ? <sup>1</sup>        | 0              |      |
| 178    | 1.0                     | 1.0                        | 2.20               | 0.48       | 0                     | 0              |      |
| 168    | 0.5                     | 1.0                        | 2.26               | 0.39       | 0                     | 0              |      |
| 170    | 0.5                     | 1.0                        | 2.18               | 0.36       | ? <sup>1</sup>        | 0              |      |

<sup>1</sup> The three questionable endosteal reactions are listed as positive in table 5.

the tibia and humerus, and certain of the soft tissues were fixed in Zenker-formol, embedded in nitrocellulose, sectioned serially and stained with hematoxylin-eosin-azure II. In many instances the corresponding bones from the opposite side of the animal were fixed in neutral formalin, sectioned after embedding in nitrocellulose, and stained, without decalcification, with silver and hematoxylin-eosin (McLean and Bloom, '40). In the earlier experiments the bones were split open

longitudinally to permit penetration of the fixative. Later they were fixed whole or cut with a dental drill for the better preservation of topographic relations. On account of the distortion incident to excentric longitudinal sections, measurements of penetration of new bone into the marrow space are given only from cross sections of the central portion of the shaft of the femur.

TABLE 4

*Effects of single dose of parathyroid extract (50 units) on pigeons. All pigeons had received  $\alpha$ -estradiol, 66.5 gamma per day for 14 days, just before administration of parathyroid extract. In addition, pigeon 28 had received 1.5 gamma per day for 8 days, and all others except 6 and 16 had received approximately 80 gamma in 32 days, just before beginning of final experimental period. Experiment was carried out during April-June, 1939, in breeding season.*

| PIGEON | SEX | TIME AFTER<br>PARATHYROID<br>EXT. | SERUM         |            | ENDOSTEAL<br>REACTION | MEDULLARY<br>BONE | OSTEOBLASTS | OSTEOCLASTS |
|--------|-----|-----------------------------------|---------------|------------|-----------------------|-------------------|-------------|-------------|
|        |     |                                   | Calcium       | Phosphate  |                       |                   |             |             |
| No.    |     | Hours                             | mM.<br>per L. | mM. per L. |                       |                   |             |             |
| 9      | C   | 3½                                | 4.81          | ....       | +                     | 0                 | Few         | Very many   |
| 27     | M   | 6                                 | 4.13          | 1.377      | +                     | +                 | Few         | Very many   |
| 14     | C   | 9                                 | 4.26          | ....       | +                     | Trace             | Many        | Very many   |
| 28     | M   | 12                                | 2.84          | ....       | +                     | +++               | Some        | Many        |
| 15     | C   | 15                                | 3.63          | 1.33       | ? <sup>1</sup>        | 0                 | 0           | Very many   |
| 30     | M   | 18                                | 2.34          | 1.15       | +                     | +++               | Some        | Very many   |
| 13     | C   | 21                                | 3.77          | 1.088      | ? <sup>1</sup>        | 0                 | 0           | Some        |
| 31     | M   | 24                                | 3.01          | 1.277      | +                     | ++                | Few         | Many        |
| 12     | C   | 27                                | 3.12          | 1.11       | +                     | 0                 | Few         | Very many   |
| 32     | M   | 30                                | 2.76          | 1.52       | +                     | +                 | 0           | Many        |
| 6      | C   | 48                                | 2.88          | 1.385      | +                     | 0                 | 0           | Many        |
| 16     | C   | 60                                | 2.425         | 0.956      | +                     | 0                 | 0           | Some        |

<sup>1</sup> The questionable endosteal reactions are counted as positive in table 5.

Serum calcium was determined by the method of Clark and Collip ('25) and serum phosphate by the method of Fiske and Subbarow ('25) upon blood obtained at the time the birds were sacrificed.

#### OBSERVATIONS

Under appropriate experimental conditions, to be described, there is formation of new bone under the endosteum, and in

TABLE 5  
*Summary of observations on bones of ninety-two pigeons from tables 1 to 4.*

|                          | TABLE 1 | TABLE 2 | TABLE 3 | TABLE 4 | TOTALS | ENDOSTEAL REACTION |    | MEDULLARY BONE |       |          |
|--------------------------|---------|---------|---------|---------|--------|--------------------|----|----------------|-------|----------|
|                          |         |         |         |         |        | 0                  | +  | 0              | Trace | + to +++ |
| Male pigeons             |         |         |         |         |        |                    |    |                |       |          |
| Controls                 |         |         |         |         |        |                    |    |                |       |          |
| Spring                   | 5       |         |         |         | 5      | 5                  | 0  | 5              | 0     | 0        |
| Fall or winter           | 5       | 1       |         |         | 6      | 6                  | 0  | 6              | 0     | 0        |
| Estradiol                |         |         |         |         |        |                    |    |                |       |          |
| Spring                   | 11      |         |         | 5       | 16     | 0                  | 16 | 0              | 0     | 16       |
| Fall or winter           | 6       | 3       |         |         | 9      | 3                  | 6  | 6              | 3     | 0        |
| Testosterone             |         |         |         |         |        |                    |    |                |       |          |
| Fall or winter           |         | 1       |         |         | 1      | 1                  | 0  | 1              | 0     | 0        |
| Estradiol + testosterone |         |         |         |         |        |                    |    |                |       |          |
| Fall or winter           |         | 9       |         |         | 9      | 0                  | 9  | 0              | 0     | 9        |
| Castrates                |         |         |         |         |        |                    |    |                |       |          |
| Controls                 |         |         |         |         |        |                    |    |                |       |          |
| Fall or winter           |         | 1       | 1       |         | 2      | 2                  | 0  | 2              | 0     | 0        |
| Estradiol                |         |         |         |         |        |                    |    |                |       |          |
| Spring                   | 2       |         |         | 7       | 9      | 1                  | 8  | 7              | 2     | 0        |
| Fall or winter           | 8       | 3       | 2       |         | 13     | 6                  | 7  | 11             | 1     | 1        |
| Testosterone             |         |         |         |         |        |                    |    |                |       |          |
| Fall or winter           |         | 1       | 1       |         | 2      | 2                  | 0  | 2              | 0     | 0        |
| Estradiol + testosterone |         |         |         |         |        |                    |    |                |       |          |
| Fall or winter           |         | 9       | 11      |         | 20     | 2                  | 18 | 4              | 2     | 14       |
| Totals                   | 37      | 28      | 15      | 12      | 92     |                    |    |                |       |          |

the medullary cavities of the long bones. The material here reported includes the very earliest stages of this phenomenon, and intervening stages up to the appearance of trabeculae of bone extending into the medulla for a distance of 0.5 mm. or more. The process is identical with that occurring in female pigeons during the early pre-ovulatory period. Table 5 summarizes the observations in ninety-two pigeons, reported in detail in tables 1 to 4.

### *Description of the bones*

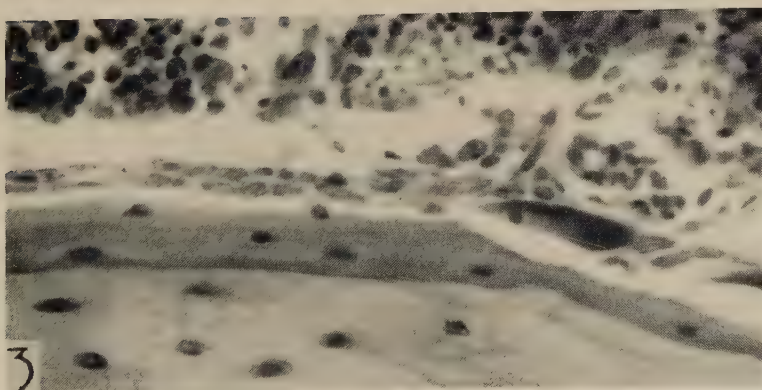
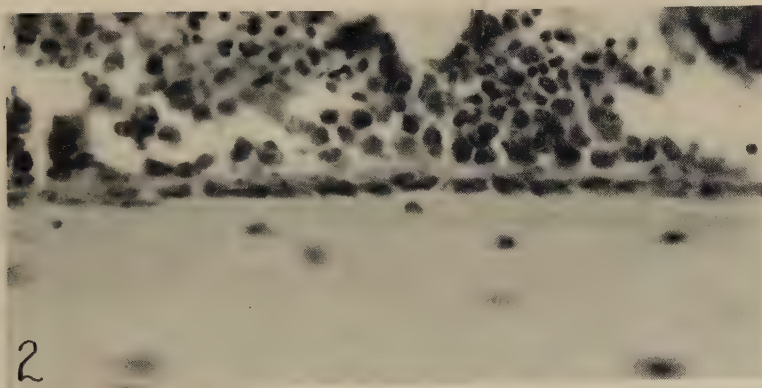
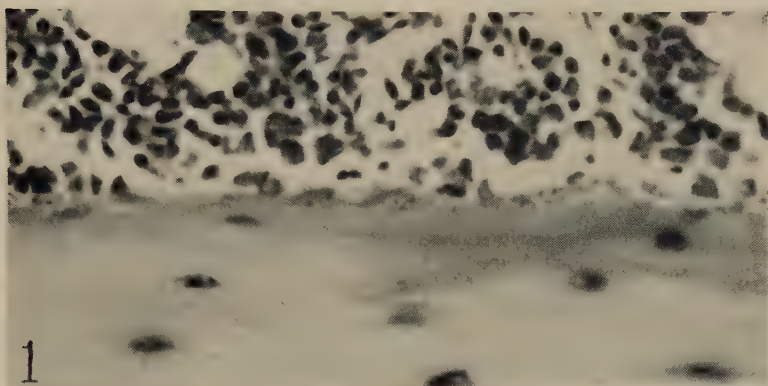
*Controls, including testosterone alone.* The findings in the bones of eleven intact and two castrate untreated male pigeons, and one intact and two castrate male pigeons given testosterone alone are identical, and are unaffected by the season. The femurs and tibias of these pigeons, like those of the female in the resting phase of the reproductive cycle, contain no bone in the medullary cavity of the shaft. When the bone is split and the marrow is removed the endosteal surface of the compact bone of the shaft is seen to be smooth and glistening, and when examined with a blunt probe no roughening of the surface is detectable. In sections of Zenker-formol fixed, decalcified bones, stained with hematoxylin-eosin-azure II, the shaft stains pink. The inner surface is usually found to be

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Fig. 1 Section in long axis of femur of untreated male pigeon no. 86 (see table 1) in June. The shaft is lined by a single layer of spindle-shaped cells, which may be regarded either as reticular cells or "resting" osteoblasts. Hematoxylin-eosin-azure II. Photomicrograph.  $\times 700$ .

Fig. 2 Section in long axis of femur of castrate pigeon no. 8 (see table 1) following 14 days of daily injections of 66.5 gamma of  $\alpha$ -estradiol. The shaft is lined with a single layer of cuboidal, basophilic osteoblasts. No new bone formation. This is a minimal "endosteal reaction." Hematoxylin-eosin-azure II. Photomicrograph.  $\times 700$ .

Fig. 3 Section in long axis of femur of male pigeon no. 40 (see table 1) following 14 days of daily injections of 66.5 gamma of  $\alpha$ -estradiol in November-December. The shaft is lined with a double layer of osteoblasts and spindle-shaped cells. Toward the right is an osteoclast overlying an area of resorption. There is a zone of endosteal bone, sharply differentiated from older bone of shaft. This is the maximum reaction seen in male pigeons in resting period, when treated with  $\alpha$ -estradiol alone. Hematoxylin-eosin-azure II. Photomicrograph.  $\times 700$ .



Figures 1 to 3

lined with a discontinuous layer of single, spindle-shaped cells, forming the endosteum (fig. 1). Usually there are no osteoblasts present, although in two of these femurs (both in the fall series) there were occasional short rows of them, and osteoclasts varied in number from many to an occasional atypical one or even none.

*The endosteal reaction.* The first observed reaction to the administration of sex hormones to male or castrate pigeons is in the endosteal lining of the shafts of the long bones (Pfeiffer and Gardner, '38 a). Instead of a single layer of spindle-shaped cells there is seen a layer of osteoblasts (fig. 2) which extends for variable distances along the inner surface of the compact bone of the shaft and is accompanied by the formation of new bone. The first new bone formed is in a thin layer (less than  $2\mu$ ) immediately under the osteoblasts, and stains pale pink with hematoxylin-eosin-azure II. This bone is applied directly upon the surface of the compact bone of the shaft, and as it increases in thickness it takes on a blue or purple stain, sharply differentiating it from the older, pink-stained bone of the shaft (fig. 3), there being frequently a sharp, blue-stained line of demarcation. The most superficial layer beneath the osteoblasts may still stain pink. At this stage the osteoblasts have also increased, so that the spindle-shaped cells of the endosteum are now replaced by osteoblasts, which in some places may form several layers of cells; these osteoblasts are often separated from the marrow by a layer of spindle-shaped cells. The bone-forming activity characterized by the osteoblastic reaction just described is always accompanied by its counterpart, i.e., resorption associated with the presence of osteoclasts, but at this stage osteoclasts are not prominent.

The process just described marks a qualitative deviation from the normal appearance in the male or castrate, and from the resting stage in the female, and is clearly recognizable as soon as new endosteal bone begins to be laid down. Under certain conditions the process does not proceed further, but is found in about the same stage whenever the animals are

examined at the end of experimental periods of 2 to 3 weeks. Because this process is clearly defined, and because its self-limitation is characteristic of certain experimental conditions, we shall refer to it in this paper as the "endosteal reaction," which includes all stages from the first response of osteoblasts to that of the deposition of a layer of new bone upon the compact bone of the shaft.

*Formation of medullary bone.* Under certain conditions the process initiated with the endosteal reaction goes on to the formation of medullary bone. This new bone, growing out from the shaft and invading the marrow, is continuous with the shaft, or more properly, with the endosteal new bone laid down in the endosteal reaction. Medullary bone was first observed in the normal female pigeon, during the preovulatory period, by Kyes and Potter ('34), and has been described in detail by Bloom, Bloom and McLean ('41).

We regard the formation of medullary bone as an extension of the endosteal reaction, reflecting a greatly accelerated rate of bone production. When new bone begins to be formed very rapidly its deposition is not confined to the endosteal surface of the shaft, but the growth is turned inward and it invades the medullary cavity (fig. 4). Presumably this "budding" or "sprouting" is initiated in areas where the osteoblastic layer is covered by and is continuous with several layers of spindle-shaped cells, since this finding is characteristic of the rapid growth of medullary bone. In laying pigeons the process continues until the medullary cavity is filled with spongy bone. In the experiments here reported we have not continued the stimulus long enough to obtain the maximum amount of formation of medullary bone, but in no case have we been able, by the administration of sex hormones, to approach the rapidity of bone formation which occurs in the pigeon during the week of maturation of the first ovarian follicle.

The new medullary bone usually stains purple or blue, as does the endosteal bone (fig. 4), in contrast to the pink-staining compact bone of the shaft. However, the thin superficial

lamellae of the most advanced portions of the spicules of bone also stain pink with hematoxylin-eosin-azure II. The newest bone has a border of osteoblasts, but where bone-form-

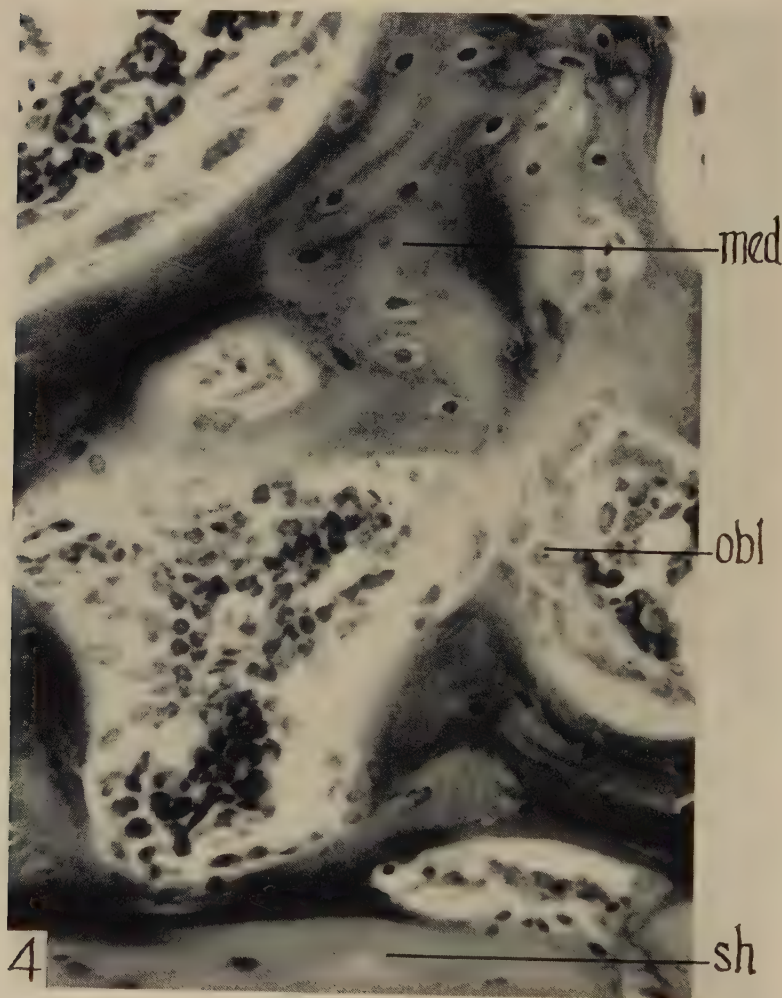


Fig. 4 Section in long axis of femur of male pigeon no. 77 (see table 1) following 14 days of daily injections of 66.5 gamma of  $\alpha$ -estradiol in May-June. The medullary bone, med, stains purple or blue in contrast with the red of the shaft, sh. There are numerous osteoblasts, obl, over parts of the surface of the medullary bone. Hematoxylin-eosin-azure II. Photomicrograph.  $\times 700$ .

ing activity has ceased, in the areas nearer the shaft, the osteoblasts are often replaced by spindle-shaped cells. When growth of bone is very active the osteoblasts project beyond the spicules of bone, and are continuous with spindle-shaped cells and reticular cells in the marrow. Although osteoblasts predominate during the stage of rapid growth, there are also areas of resorption of bone, accompanied by osteoclasts.

We have endeavored to give quantitative expression to the amounts of medullary bone formed under the conditions of our experiments, the best criterion being a rough average of the depth of penetration of the marrow, by the spicules of new bone, as seen in cross section. There is also some variability in the number of trabeculae, and in their total mass, but these variables are in general correlated with the depth of penetration.

In undecalcified preparations, impregnated with silver nitrate, and in agreement with the findings in medullary bone formed spontaneously during the egg-laying cycle, no uncalcified osteoid tissue is seen on the surfaces of the trabeculae of medullary bone, which is calcified as it is laid down.

*Influence of season and of castration upon response  
to estradiol*

*Estradiol in intact males in the spring.* In every case in which  $\alpha$ -estradiol alone was given to normal male pigeons in the spring (tables 1 and 5), usually in doses of 66.5 gamma per day for not less than 14 days, new medullary bone developed, reaching well into the marrow cavity of the femur, the mass of new bone and the depth of penetration into the cavity being correlated roughly with the length of time the hormone was administered.

*Estradiol in intact males in the fall and winter.* When the above observations were repeated upon intact male pigeons in November and December (tables 1, 2, 5), the results were strikingly different. Out of nine pigeons given  $\alpha$ -estradiol in doses of 66.5 gamma per day for 13 to 21 days, in three the

histological picture is identical with that in the untreated controls. In six of the pigeons there is a recognizable endosteal reaction, but in only two is there a definite, but very slight outgrowth of new bone into the marrow cavity, measureable in hundredths rather than in tenths of a millimeter (table 2).

*Estradiol in castrate males in the spring.* When castrate males were given  $\alpha$ -estradiol in the spring, in the same doses and over the same periods of time as for the intact males (tables 1, 4, 5), seven out of nine produced no new medullary bone, and the other two only very small amounts. In the latter the medullary bone consisted of only three or four short thin spicules projecting in from a very irregular endosteal surface. Of the seven birds in which no medullary bone was demonstrable, four showed a definite endosteal reaction, two, a questionable one, and one the same histological picture as the uninjected controls, i.e., a smooth endosteal surface.

*Estradiol in castrate males in the fall and winter.* Out of thirteen castrate males given  $\alpha$ -estradiol in the fall and winter in doses comparable to those given in the spring (tables 1, 2, 3, 5), six showed findings identical with those of the untreated controls. Seven showed endosteal reactions, but of these there was formation of medullary bone in only two. Of these, in one new bone was present only in minute amounts.

One of the castrate males, given 50 gamma of  $\alpha$ -estradiol per day for 14 days, or a total of 700 gamma, requires special mention. In contrast to twelve other castrate males, similarly treated, this pigeon produced medullary bone in as large amounts as did any other pigeon reported in this paper. We are unable to account for this discrepancy.

#### *Influence of testosterone upon response to estradiol*

*Estradiol and testosterone in intact and castrate males in the fall and winter.* In view of the suggestion arising out of the foregoing experiments that the male hormone, as well as estrogen, is essential to the formation of medullary bone, an experiment was devised to test this hypothesis (table 2). The dosage of  $\alpha$ -estradiol was kept constant at 66.5 gamma per

day, and testosterone propionate was given in doses of 0.5, 1.0, and 2.0 mg. per day, both intact and castrate male pigeons being used. The results are in striking confirmation of the hypothesis. While intact males and castrates gave a minimal or no response to estradiol alone, all of the animals given 0.5 mg. of testosterone propionate per day or more reacted to at least the same degree as did males given estradiol alone during the period of sexual activity in the spring. The maximum effect of testosterone appeared to be produced by daily administration of 1.0 mg. of the propionate.

*Testosterone with decreasing doses of estradiol in castrate males.* Since we had shown that androgen, in addition to estrogen, is essential to the production of medullary bone in the castrate pigeon, an experiment was planned (table 3) to determine whether the dosage of estradiol necessary to produce this reaction might be markedly reduced by the administration of testosterone propionate in optimum amounts (1.0 mg. per day). Under these conditions a good response was obtained with doses of  $\alpha$ -estradiol as low as 5 gamma per day, with an endosteal reaction at 2.5 gamma per day, but there was a considerable diminution in the response with reduction of the dosage from 50 gamma to 10 gamma per day. At 1.0 gamma per day or less there was no appreciable endosteal reaction, and of course no formation of medullary bone.

#### *Other hormonal influences*

*Effects of parathyroid extract.* Table 4 summarizes the effects of administering parathyroid extract, in uniform single doses of 50 units, given intramuscularly, to male and castrate pigeons previously given large doses of  $\alpha$ -estradiol. The object of reproducing the histological picture seen in the medullary bone of laying pigeons during the periods of rapid resorption of bone was not wholly realized, but some resorption of bone, accompanied by an osteoclastic reaction, was observed in nearly every instance. The osteoclastic reaction was not confined to those birds (intact males) which had produced appreciable amounts of medullary bone, but was seen

also along the endosteal surface of the shaft, which in each instance displayed the endosteal reaction to estradiol above described.

In those castrates in which some hours had elapsed between injection of parathyroid extract and sacrifice of the animal, the bone no longer showed a typical endosteal reaction. The surface was very rough and uneven, but no characteristic osteoblasts were observed, although many of the numerous osteoclasts were basophil, and transition forms between osteoblasts and spindle-shaped cells were seen. In most places, instead of the purple or blue-staining band along the shaft, characteristic of the endosteal reaction, there was the typical pink of older, compact bone. We interpret these findings as indicating that there had been an endosteal reaction, but that there had been a reversal of this activity under the influence of parathyroid extract.

*Influence of sex hormones on the serum calcium and phosphate levels.* Although it is generally agreed that large doses of estrogens, administered to birds, will produce hypercalcemia comparable to, or even exceeding, that observed during the egg-laying cycle, the physiological significance of this experimentally produced hypercalcemia is still questioned (Marlow and Richert, '40).

Tables 2, 3 and 4 summarize the data obtained on the serum calcium and phosphate levels in the experiments here reported. From table 2 it is seen that the serum calcium level is significantly increased in all of the groups of pigeons given 66.5 gamma of  $\alpha$ -estradiol daily for 2 to 3 weeks, although in a few individual pigeons there is little or no increase. There appear to be no significant differences between the intact males and the castrates. Testosterone propionate, in increasing doses, did not enhance the hypercalcemic effect, and may even have inhibited it slightly, although the data are not adequate to draw the latter conclusion.

From table 3 it will be seen that out of three pigeons receiving 50 gamma of estradiol per day for 2 weeks, one with and two without testosterone, only the pigeon receiving testo-

sterone responded with a recognizable hypercalcemia. At no levels of  $\alpha$ -estradiol below 50 gamma per day is there hypercalcemia. The data in table 4 do not permit any conclusions as to how much of the hypercalcemia recorded is the result of estradiol, and how much of parathyroid extract. The data on serum phosphate in tables 3 and 4 are scattering and indicate no definite trend.

The data show also a dissociation of the two effects of the sex hormones studied — elevation of the serum calcium and production of endosteal or medullary bone. Administration of large doses of  $\alpha$ -estradiol (50 gamma or more daily) to male or castrate pigeons usually results in an increase in the concentration of calcium in the serum, but unless the testes are functionally active or androgen is administered little or no formation of new bone occurs. On the other hand, administration of much smaller doses of  $\alpha$ -estradiol (5 to 10 gamma per day), if given together with 1.0 mg. of testosterone propionate daily, leads to production of new endosteal and medullary bone without elevation of the serum calcium level.

*Effects of sex hormones on the testis.* In connection with the seasonal variations in bone production under the stimulation of estrogens it is interesting to note some variations in the testis. The testes of pigeons injected with estradiol in the spring are larger than those from pigeons treated in the fall, and this is also true of the uninjected controls. In addition, the testes of the injected birds are smaller than the corresponding controls, both spring and fall.

The testes of the uninjected controls in the spring have large seminiferous tubules, each of which surrounds a fair-sized lumen. There is active spermatogenesis in all of these, and a great many mitoses are noted in spermatogenic cells of all stages of development. In contrast to these testes, those of the uninjected males in the fall contain very few spermatozoa, although there are still many mitoses in the spermatocytes. The lumen is now greatly reduced in size. Estradiol injections in the spring produced this same picture in the testes of four of the pigeons, while seven others still showed

spermatogenic activity. The testes of the estradiol-injected birds in the fall gave evidence of greatly depressed activity. In these the tubules are shrunken in size, the lumen has disappeared, and vacuolated interstitial cells frequently appear in clumps between the tubules; the number of mitoses varies from a fair number in some to practically none in most of them, and there is no spermatogenesis.

The injection of testosterone caused a marked shrinkage in size of the testis. However, when both  $\alpha$ -estradiol and testosterone were administered, the testis was found at autopsy to be about the same size as had been noted before the injections were begun. These differences were borne out by microscopic examination. The testis of a pigeon which received only testosterone has greatly contracted tubules which are compressed against one another, no lumen is visible, there is practically no spermatogenesis and only a fair number of mitoses; giant cells are prominent. When the largest dose of testosterone, 2 mg. per day, was given in conjunction with estradiol, the testis remained more nearly normal. Some of the tubules are slightly contracted, there is a fair amount of spermatogenesis, many mitoses, few giant cells or other abnormal types, interstitial cells are not prominent, and the lumen is generally normal in size. As the dose of testosterone decreased, there was a gradual transition in appearance of the testis to that of the inactive organ already described. Our observations corroborate those of Pfeiffer and Gardner ('38 b).

#### DISCUSSION

There is already a considerable volume of literature on the production of medullary bone in birds under the influence of estrogens (chicken: Zondek, '37; Landauer, Pfeiffer, Gardner and Man, '39; pigeon: Pfeiffer and Gardner, '38; duck: Landauer, Pfeiffer, Gardner and Shaw, '41). To this literature the present paper adds the demonstration of a seasonal influence upon the phenomenon as induced in male pigeons, and correlates this seasonal influence with the well-known seasonal fluctuations in testicular activity. Further

evidence of the role of androgen in the process is brought forward by the findings that intact male pigeons, which fail to respond to estrogen in the fall, do so if testosterone is added, and that the same influence of testosterone is found in estradiol-injected castrate pigeons, which gave only a minimal response to estradiol alone. A similar synergistic effect of estrogen and androgen has not been found for other birds (sparrow: Pfeiffer, Kirschbaum and Gardner, '40; duck: Landauer, Pfeiffer, Gardner and Shaw, '41; chicken: Landauer, Pfeiffer, Gardner and Man, '39). For the present, therefore, the role of androgens in the production of medullary bone can only be discussed with reference to the pigeon.

Administration of estrogen to adult male or castrate pigeons leads to a resumption of osteoblastic activity at the endosteal lining of the shafts of the long bones, and for the production of this "endosteal reaction" administration of androgen may not be necessary. Unless androgen is administered, however, the response is absent or minimal, rarely leading to more than deposition of relatively small amounts of endosteal bone. When testosterone propionate is simultaneously administered a marked response is uniformly obtained, leading to the formation of trabeculae of spongy bone extending out into the marrow space.

That a minimal response is obtained by  $\alpha$ -estradiol alone, even in the absence of the testes, does not exclude the possibility that androgens are necessary for the process to occur at all. Substances with androgenic activity are produced elsewhere in the body, notably in the adrenal cortex (Hooker and Collins, '40), and the possibility that such substances are involved in the reaction is not excluded. Since androgens are also produced in the ovary there remains the possibility that they are concerned in the formation of medullary bone during the egg-laying cycle. Moreover, species differences in the non-testicular production of substances with androgenic activity may conceivably account for the differences noted above in the need for administration of androgens for the production of bone by various birds.

In addition to the formation of medullary bone, characteristic of the reproductive cycle in birds, an increase in the concentration of calcium in the serum occurs at the same time. We have discussed the elevation of the serum calcium in another place (Bloom, Bloom and McLean, '41), and have pointed out that the hypercalcemia of laying birds bears no immediate relationship, either in mechanism or in the fractions of serum calcium involved, to the hypercalcemia of hyperparathyroidism. From the data here reported it is evident that, although administration of testosterone to castrate pigeons makes it possible to produce medullary bone with relatively small doses of estradiol, there is no similar synergistic effect upon the hypercalcemia produced by estradiol, the latter occurring only after large doses of estradiol and the effect not being enhanced by testosterone. Consequently it is possible, under appropriate experimental conditions, to produce either medullary bone formation or hypercalcemia separately, or both together, thus leading to the conclusion that these two phenomena are not necessarily physiologically interdependent. Moreover, in spite of the marked enhancement of the formation of medullary bone by administration of testosterone, and in spite of the large doses of both estrogen and androgen used in our experiments, bone formation has proceeded much more slowly than during the preovulatory period in the normal female pigeon. For all of these reasons it would appear unlikely that the mechanisms responsible for bone formation and hypercalcemia in the normal female have been completely elucidated by their partial experimental reproduction following administration of estrogen and androgen.

#### SUMMARY

1. Doses of  $\alpha$ -estradiol sufficient to produce new bone in the medullary cavity of the femur of male pigeons during the breeding season are ineffective in male pigeons during the resting season, and in castrate males at any time.

2. When testosterone propionate is administered simultaneously with  $\alpha$ -estradiol, new medullary bone is formed in the femur, without regard to the presence or functional state of the testes. Under these conditions medullary bone may be formed in castrate pigeons following administration of as little as 5 gamma of  $\alpha$ -estradiol per day.

3. The hypercalcemia induced in pigeons by the administration of large doses of estrogen is independent of the simultaneous administration of androgen. It can be produced in castrate male pigeons without the occurrence of medullary bone formation, and on the other hand doses of estrogen adequate to produce medullary bone when given together with testosterone may not result in elevation of the serum calcium level.

4. The early stages of the response of the endosteum to administration of sex hormones to pigeons are described. An initial "endosteal reaction," which sometimes follows the administration of estrogen alone, consists of osteoblastic activity at the endosteal surface of the compact bone of the shaft, resulting in deposition of a few lamellae of endosteal bone. An acceleration of the process, with rapid formation of bone branching out into the marrow, requires the synergistic effect of androgen.

5. Formation of new bone, under the influence of experimentally administered estrogen and androgen, proceeds at a much slower rate than in the normal female during the pre-ovulatory period. It thus appears that the experimental conditions in male pigeons have not completely reproduced the normal physiological cycle in the female. Similar considerations make it appear unlikely that the hypercalcemia of the egg-laying cycle is completely explained by the physiological action of estrogens alone.

6. The effects of parathyroid extract on the bones of pigeons to which estradiol had been previously administered are described.

7. The growth and spermatogenic activity of the testis are inhibited by the action of either estrogen or androgen. Most

of this inhibition is prevented by the simultaneous administration of both hormones in appropriate amounts.

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## TWO HERMAPHRODITIC RATS

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TWO PLATES (TEN FIGURES)

Although immense numbers of rats and mice have been autopsied in scientific laboratories, the condition of hermaphroditism had never been reported in rats at the time that these specimens were found<sup>1</sup>, and there are only three recorded instances in the laboratory mouse (Danforth, '27; Blotevogel, '32; and Fekete, '37). The purpose of this report is to describe two instances of spontaneous true hermaphroditism (one lateral and one unilateral) which have been found in the common laboratory albino rat. Both animals were found in the same strain of rats but they were not related. Permanent modification of the external and internal genitalia in female rats has been produced experimentally by prenatal treatment with sex hormones (Hain, '35; Greene, '37; Hamilton and Gardner, '37; Greene and Ivy, '37; and Greene, Burrill and Ivy, '38, '39, '40). It is, therefore, of importance to note that the mothers of these hermaphrodites received no treatment.

The first specimen presented an ovary in the normal position on the right and a testis on the left (fig. 1). This animal, aged 28 days at autopsy, had been treated during the previous

<sup>1</sup> These are the specimens referred to by Asdell, Hamilton and Hummel ('41), in an article on hermaphroditism in the field mouse. Subsequently Burrill, Greene and Ivy ('41), published a case of spontaneous intersexuality in the rat which described a condition almost identical with one of my cases. The specimens described here were found in rats being treated or operated upon in connection with experiments being carried out in the laboratory of Dr. Frederick L. Hisaw, Harvard University, previous to 1938.

5 days with an unfractionated pituitary gonadotropic extract. The ovary contained mature follicles and corpora lutea (fig. 2) but these were undoubtedly present as a consequence of the injection. The testis could be pushed into the scrotal sac but judged by the poorly developed condition of the seminiferous epithelium (fig. 5) it probably had been in a partially cryptorchid position. The testis was misshapen; one pole was smaller than the other and was bent sharply away from the long axis of the (viscus) testis (fig. 1 a). The müllerian duct derivatives were absent on the left but on the right there was a uterine horn (fig. 1) that terminated cephalad in an oviduct and caudad in a short vagina (fig. 4). The latter was attached to the urethra dorsal to the neck of the bladder. The vagina communicated with the urethra through a small patent orifice on the median aspect of the colliculus seminalis. The uterus (fig. 3) was distended with fluid and the vagina was cornified. The cervix uteri (fig. 4 a) was represented by a narrow band of tissue (with no cervical glands) extending inward from one side of the müllerian duct at the junction of the uterus and vagina so as partially to occlude the lumen. The left vas deferens and epididymis were normal but on the side with the female structures the vas deferens was located in the mesometrium (fig. 3) and was continued cephalad as the epididymis which was located lateral to the ovary (fig. 1). The convolutions of the oviduct were grouped together in the right epididymis. The vasa deferentia each terminated caudad in an ampulla through which communication with the urethra was established. The seminal vesicles were bilateral and each had a terminal flexure (fig. 1). The prostate lobes were similar to those of a normal immature male rat as was also the paired Cowper's glands and coagulation glands. The external genitalia were not characteristic of either sex. A marked hypospadias was present and the ridge formed by the anterior cartilaginous process of the os priapi was prominent in the urethral cleft (fig. 1). There was no glans penis or prepuce. The vaginal aperture was absent.

The second hermaphroditic specimen was taken for a male and was revealed when a bilateral castration was attempted. The animal was immediately killed. It was 70 days of age and had not been previously treated. There was an ovotestis on the right at the base of the kidney and a scrotal testis on the left (fig. 6). The ovotestis was a firm pea-sized body attached to the right caput epididymis. It contained degenerate seminiferous tubules and there was a small group of graafian follicles in one place on the surface (fig. 7). None of these follicles were luteinized. The müllerian derivatives were confined to the right side (fig. 6) and consisted of an oviduct, a uterine horn and a short vagina. The latter was attached to the urethra dorsal to the neck of the bladder (fig. 9) and communicated with the urethra through a very small orifice on the dorsal aspect of the colliculus seminalis. The uterus was large but was not distended with fluid. The vaginal epithelium was mainly mucified but in some areas cornified layers were being desquamated (fig. 9). The cervix uteri was identical with that seen in the previous specimen. The testis and epididymis on the left were not in any way abnormal. The disposition of the vasa deferentia (figs. 6 and 8) was identical with that noted in the previous specimen. The right epididymis was remarkably well formed considering the nature and small size of the right gonad; the convoluted oviduct was embodied in the epididymis. There was also a cyst in the caput epididymis which probably represented a vestigial mesonephric tubule (epoöphoron). The full complement of well developed male accessory sexual glands was present. The external genitalia were strictly masculine; there was no sign of a vaginal introitus. The phallus was not underdeveloped and it displayed a retractable prepuce, a glans (with papillae) and os priapi. Since the testis was producing spermatozoa (fig. 10) and androgens were being secreted, there is no reason to believe that the hermaphroditic condition would have been a handicap to procreation had this animal been mated with normal females.

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## PLATES

## ABBREVIATIONS

|                         |                                  |
|-------------------------|----------------------------------|
| b., bladder             | s. a., internal spermatic artery |
| c., Cowper's gland      | s. v., seminal vesicle           |
| e., epididymis          | t., testis                       |
| ov., ovary              | u., urethra                      |
| ov. t., ovotestis       | ut., uterus                      |
| p., penis               | ur., ureter                      |
| p. d., dorsal prostate  | v., vagina                       |
| p. v., ventral prostate | v. d., vas deferens              |

## PLATE 1

### EXPLANATION OF FIGURES

1 Dorsal view of the reproductive system of a hermaphrodite rat which was 28 days of age at necropsy. The planes through which the histological material, illustrated in figures 2 to 5, were obtained are indicated.

1 a Another view of the left testis showing its abnormal shape.

2 A section of the right gonad showing that it is an ovary. The corpora lutea and large follicles were undoubtedly present as a result of treatment with pituitary gonadotropic extract.

3 A cross section of the male and female ducts on the right. The vas deferens was parallel with the uterus and may be seen in the mesometrium.

4 A sagittal section through the cephalic end of the urethra showing the attachment of the vagina to the urethra dorsal to the neck of the bladder. Cornified cells can be seen sloughing off into the vagina.

4 a A longitudinal section through the caudal end of the uterus showing the abnormal cervix uteri.

5 Showing the seminiferous tubules and interstitial cells in testis.





6 Ventral view of the reproductive system of a hermaphrodite rat which was 70 days of age at necropsy. The planes through which the histological material, illustrated in figures 6 to 10, were obtained are indicated. The seminal vesicle on the right is hidden from view.

7 Showing a portion of the right gonad. Graafian follicles are evident on the surface and subjacent to these may be seen the very degenerate seminiferous tubules which made up the bulk of this gonad.

8 A cross section of the male and female ducts on the right side. The vas deferens was parallel with the uterus and may be seen in the mesometrium.

9 A sagittal section through the cephalic end of the urethra showing the attachment of the vagina to the urethra dorsal to the neck of the bladder.

10 Showing the microscopic structure of the left testis. Spermatozoa are present in the tubules and the interstitial cells are identical with those of normal male rats of similar age.

## BOOK REVIEW

INTRODUCTION TO VERTEBRATE EMBRYOLOGY. Waldo Shumway. John Wiley & Sons, 1942 (\$4.00).

The prime function of a college textbook of vertebrate embryology is to present the fundamental concepts of maturation, cleavage, germ layer formation, and organogeny in such a manner as to be at once clear, scientifically accurate, and sufficiently complete as to form a basis for graduate work in the field or for a clearer appreciation of medical school embryology. In this regard the fourth edition of Shumway's "Introduction to Vertebrate Embryology" is definitely a forward step. Rather than to isolate the various vertebrate forms and consequently confuse the student by emphasizing what are often only minor differences, the approach here is to treat one phase of the embryological process (i.e., the development of the digestive system) in such a manner as to emphasize the fundamental similarities of the one process in the different forms. By this method one does not lose sight of the differences between, for instance, holoblastic and meroblastic cleavage, or gill and lung formation, but rather each difference is explained on a perfectly logical basis and is therefore understood and remembered the better.

The particular advantage of this new edition, however, lies in the author's copious use of illustrative material, much of which is entirely new. It is very important that the student gain a three-dimensional perspective of embryonic development and this is materially aided by the drawings of whole embryos and photographs of sections. Specifically, Shumway has added drawings of the normal stages of amphibian development and has placed photographs alongside some of the drawings. One could wish for better reproduction of some of these photographs but they nevertheless convince the student of the accuracy of the drawings. A student trained with adequate illustrative material will not be limited to certain classical series of drawings but will rather have in mind the three-dimensional embryo as a whole.

Instead of scattering references to experimental embryology throughout the text, as was done in the previous edition, the author has concentrated this material in one chapter. The alert student's curiosity will very definitely be aroused by this chapter. While basic

embryology is very important (as is a Dictionary!) it needs vitalizing by means of brief and pertinent reference to variations in normal development brought about by experimental procedures. There is no justification for overemphasizing teratologies but any student is likely to become more interested in, and amazed by, normal embryonic development and consequently understand it better if he knows what might happen, for instance, when two blastomeres are separated from each other at the two cell stage.

One gets the impression that in 246 pages Shumway has condensed the essential features of early vertebrate embryology about as far as it is possible without justifying the criticism of over-simplification. In the remaining 78 pages he touches on the high spots of experimental (amphibian) embryology; gives some 57 fully labelled drawings of sections of frog, chick, and pig embryos; and finally presents some 500 embryological terms briefly defined. The general impression, therefore, is that the controversial points of purely descriptive embryology have been less emphasized in favor of presenting the more important basic principles in less space and adding some of the practical information which will help the advanced undergraduate student to "get his teeth into" the subject matter of vertebrate embryology.

ROBERTS RUGH

GEORGE ELLETT COGHILL  
1872-1941

IN MEMORIAM<sup>1</sup>

“The way to build a university is from the top down.” This aphorism, quoted by Doctor Coghill from his first teacher of science, may be recast to apply to his own career, which was unique in several respects and particularly in the way it was built from specifications definitely formulated in advance. With most of us probably the programs of research were built up by slow accretion as we grew in knowledge and as opportunity opened; the ideals toward which we work were gradually matured in the light of experience acquired. With Coghill the definitive objective was clearly envisaged and the broad outlines of the program were laid down before he even began his scientific training. The pursuit of this remote objective was never relaxed and the guiding light of his original ideal was never dimmed during all those years of laborious drudgery devoted to fact-finding and correlation of the data. The career was built from the top down in the sense that every step taken, every line of inquiry begun, was directed toward a definite end and was set in its appropriate place without fumbling or lost motion.

At twenty-five years of age, after a conventional classical training at Brown University, he made the painful discovery that the professional career for which he had prepared himself could not be continued without sacrifice of intellectual honesty and independence. Baffled and discouraged, he sought another outlet for his craving to do something constructive in the field of public service. His distress arose from a conflict

<sup>1</sup> Presented at the fifty-eighth session of the American Association of Anatomists, at New York, April 1, 1942.

between his own way of independent thinking and the traditional dogmas and irrational intolerance of both the academic and the lay public of his midwestern community. This was obviously a psychological difficulty, so he resolved to strike at its roots and to devote himself to a systematic investigation of the natural history of the human mind. He sensed at once that this is essentially a biological problem whose key factors lie in the nervous system.

As opportunity opened, he served a three-year apprenticeship from 1897 to 1900 under the guidance of the late C. L. Herrick, then president of the nascent Territorial University of New Mexico. This was a fortunate association, providing training in elementary biology, the exacting technique of neuroanatomy, sound research methods, up-to-date problems and methods of experimental and comparative psychology, and broad philosophical background. His teacher was actually engaged in the enterprise of building a university, starting at scratch, from the top down, and the neophyte profited by the example and planned his own program on similar principles.

The nervous system was envisaged as a going concern whose structure can be understood only in terms of actual performance of bodily work. Accurate knowledge of this structure being a prime consideration, he returned to his Alma Mater and in 1902 published a dissertation on the cranial nerves of *Amblystoma tigrinum*. The choice of this theme showed insight, for it involved a study of the entire body of the animal. Since the organism as a whole in relation with environment was the object of study, this dissertation laid a secure foundation for all subsequent work. Through the subsequent years the program included, not only his own research upon the nervous system, but also preliminary studies, with his pupils, on the parallel development of blood vessels, organs of digestion, excretion, etc. The exactions of teaching and other duties prevented the completion of these studies, but it is probable that, if the program of collaboration with other workers so auspiciously begun at The Wistar Institute in 1926 had continued throughout the ten years of his

incumbency there, these investigations would have been resumed. In view of the enormous amount of research which has been done on *Amblystoma*, it is very desirable that the development of all systems of organs of this critical type be carefully studied in correlation with Harrison's stages of growth and Coghill's sequence of behavior patterns. This is logically the next step toward the realization of Doctor Coghill's ideal.

Such studies are pertinent here because the most significant outcome of the whole series of Doctor Coghill's researches is the impressive demonstration of the essential unity and integrity of the organism and the dominance throughout life of "total patterns" over "partial patterns" of behavior. The failure of some current studies of nervous physiology to realize this is responsible for futile attempts to interpret animal behavior as a mere summation of particular patterns of isolated parts. For instance, the most exact knowledge of what is going on in peripheral nerve fibers during excitation cannot be applied without qualification to the resolution of the problems presented in the central adjustors, and some so-called spontaneous behavior may be related with disturbance of the endocrine balance.

The task to which young Coghill proposed to devote his life was an investigation of the bodily apparatus which actually performs the work manifested as animal and human behavior. At the turn of the century direct examination of nervous tissue in action was impossible; the electrical and other methods now available had not been devised. But overt behavior was observable, so in 1904 he conceived the idea of following the growth of some typical vertebrate from pre-motile stages to adult, observing first the successive changes in behavior and then examining microscopically a series of tested specimens of known physiological age to discern the sequence of structural changes correlated with the changes in behavior.

*Amblystoma* not being at the time available, the first physiological observations were made upon *Triturus* (*Diemyctylus*)

torosus, and these were subsequently repeated with *Amblystoma*. *Triturus* again was a fortunate selection, for Doctor DuShane has recently found that the development of this species resembles very closely that of *Amblystoma punctatum*. In this report on the reactions of *Triturus* in 1909 Doctor Coghill wrote, "tabulated schemes for rapid recording were tried in my first experiments of 1906, but it soon became apparent that such forms could not be adhered to, for they were necessarily based upon presumptions of some sort and were, therefore, a hindrance rather than a help to alert observation." This is typical; conventional methods and traditions were discarded and the entire program was carried through with an originality of method and distrust of dogma which held him down to his evidence and ultimately led to conclusions of far-reaching significance. The observations on *Triturus* were so unique and the charts recording them were so unconventional that one of the editors of the journal to which the paper was submitted objected to its publication.

While holding college appointments from 1902 to 1913 and at the University of Kansas, 1913 to 1926, he worked ardently on *Amblystoma*, testing large numbers of individual specimens under continuous observation for several days and nights. These very exacting studies which yielded the statistical norm of the sequence of physiological development have not been published in detail, but the complete records are among his papers and it is hoped that an adequate summary of these data may be assembled for publication.

Most of the publications of this period, 1902 to 1926, are in Parts 1 to 6 of his "Correlated Studies," which relate chiefly to the internal structure of the spinal cord and brainstem. The specimens here described were all individually tested and of known physiological age. These studies were continued at The Wistar Institute up to 1931 with the publication of no. 10 of the series, which summarizes and interprets the findings. Papers 11 and 12 followed in 1933 and 1936, beginning a systematic study of the differentiation of the

limbs and their activities as an example of the relation of local reflexes to the "total pattern" of behavior.

During the decade at The Wistar and thereafter, despite failing health and serious disabilities, he published also many short papers on the more general aspects of his problem which give suggestions, but no systematic exposition, of the broad philosophical conclusions to which his studies pointed. He was much in demand for lectures, though failing strength unfortunately soon put an end to this very stimulating activity. So fruitful for psychology are these studies that near their close Arnold Gesell wrote,

"Although Coghill has not made a single experiment in psychology, in the orthodox sense, he has already had a profound influence on the biological interpretation of psychological problems. His three lectures on 'Anatomy and the Problem of Behavior,' delivered in London, bid fair to become classic. The thin volume which contains them belongs on a five foot shelf."

Doctor Coghill was elected to membership in this Association in 1904 and was our president from 1932 to 1934. His presidential address at the meeting of 1933 in Cincinnati, entitled "The neuro-embryologic study of behavior: principles, perspective and aim" (published in *Science* for August 18, 1933), shows profound insight into the philosophical significance of his observations, concluding with the remark, "If this be philosophy, I would call it a philosophy, not of *being*, but of *becoming*; not of *life*, but of *living* — which is itself my supreme experiment."

He was a member of the National Academy of Sciences, the American Philosophical Society, and many others. On the occasion of the presentation to him of the Elliot Medal of the National Academy of Sciences, April 24, 1934, Doctor Harrison said,

Doctor Coghill's pioneer work has won for him a place of high distinction. . . . It has been found that a progressive differentiation of nerve cells, fibers and sense organs takes place, preceding by a short interval the initiation of the cor-

responding reactions. Associated with differentiation, but in a certain sense antagonistic to it, is the process of growth, the study of which has required the counting of thousands of cells and charting their positions in the spinal cord and brain at various stages of development. This has involved an immense amount of painstaking work which would all have been to little purpose, had the task not been approached by a man of broad knowledge and subtle insight. From all this has developed a new conception of the origin of nervous function. . . . These investigations of Doctor Coghill will have a lasting influence in psychology and physiology as well as in embryology."

Doctor Coghill was born at Beaucoup, Illinois, March 17, 1872; he died at Gainesville, Florida, July 23, 1941. Reared on a farm where severe discipline, incessant toil, and some hardships were the order of the day, he early developed the stability of character, rugged honesty, tenacity of purpose (and sometimes, alas! inflexibility in adjustment to people of less rigorous standards) which were the dominant traits of his personality.

In 1930 his health began to fail under the strain of work and anxiety and from June, 1934, until he left The Wistar Institute near the end of 1935 he experienced cardiac attacks of varying severity. Nevertheless the research program was carried on with the aid of his faithful assistants as long as their services were available, and even the last years in retirement in Florida were productive. Though enfeebled and at times wholly incapacitated, he pluckily continued to work as strength allowed.

Here he not only continued his studies of *Amblystoma* but expanded the program to include the newborn opossum, because in this species the precocious development of the limbs promised data of importance in his studies of the origin of limb reflexes. On several occasions younger colleagues visited him to collaborate upon some phase of the broad program. So intriguing was his personality and so helpful his suggestions that several students at the University of Florida undertook on foot the trek from campus to "The Singing Pines," as

Coghill called his home a few miles out of Gainesville, carrying their microscopes, to spend time with their friend, to examine his slides and to absorb his philosophy.

During most of this time one or another of his devoted children was with him. The end came suddenly and unexpectedly, removing a great man, a preeminent student of nature, and a good friend from among us. An appreciation, with portrait and bibliography, was published in *The Journal of Comparative Neurology*, October, 1941.

C. JUDSON HERRICK

D. S. PANKRATZ

# PROCEEDINGS OF THE AMERICAN ASSOCIATION OF ANATOMISTS

## FIFTY-EIGHTH SESSION

*Cornell University Medical College  
New York City  
April 1, 2 and 3, 1942*

The Fifty-eighth Meeting of the Association, by invitation of Cornell University Medical College, was held in the Hotel Commodore and at the Cornell University Medical College, Wednesday April 1, Thursday April 2 and Friday April 3. The Demonstrations were conducted at the Medical College; all other sessions at the Hotel Commodore. The Local Committee was comprised of J. F. Nonidez, C. V. Morrill, G. N. Papanicolaou, C. L. Yntema, W. S. Hammond, C. O. Warren, C. Berry, J. MacLeod, W. A. Geohegan, and J. C. Hinsey, Chairman.

### *Registered attendance*

|                     | 1942 | 1941 |             | 1942 | 1941 |
|---------------------|------|------|-------------|------|------|
| Association members | 226  | 350  | Out of town | 309  | 380  |
| Non-members         | 201  | 134  | Local       | 118  | 104  |
|                     | —    | —    |             |      |      |
| Total registered    | 427  | 484  |             |      |      |

## RESUME OF THE SCIENTIFIC PROGRAM

The Fifty-eighth Session of the American Association of Anatomists was opened in general session by President Philip E. Smith at 10:00 A.M., in the East Ballroom of the Hotel Commodore. Following the announcement of Auditing and Nominating Committees, six scientific papers were presented. At 11:45 the Association paid tribute to a former President,

George Ellett Coghill, through a memorial prepared by C. J. Herrick and D. S. Pankratz, and read by Davenport Hooker. After a 15-minute recess, the *Presidential Address* was given by President Philip E. Smith on the subject: "Some aberrant responses to sex hormones."

The remainder of the program was divided into (a) Sessions for the reading of papers: Wednesday afternoon 2:00 to 5:00; Thursday morning 9:30 to 12:15; Friday morning 9:30 to 1:00; (b) A session of demonstrations Thursday afternoon 2:00 to 5:30; (c) A session for motion picture demonstrations Wednesday evening 7:15 to 9:00; and (d) a general session with an invitation program Friday afternoon 2:00 to 4:00. On Wednesday afternoon and Friday morning there were four and on Thursday morning three, concurrent sessions. (The Secretary would have preferred to schedule four on Thursday and three on Friday, but was unable to obtain the fourth assembly room on Thursday.)

The restricting of regular demonstrations to a single afternoon was decided upon because of the distance of the Cornell Laboratories, where the demonstrations were held, from the Hotel, where the papers were presented. By arranging a special Wednesday evening session for the motion pictures, the regular demonstrations were left without competition. An exceptionally attractive feature of the afternoon was the scheduling of demonstrations, by members of the Cornell Anatomy Department, in their private laboratories, of the wealth of interesting work and of unusual apparatus used in investigation, which bear evidence to the continued productiveness under Prof. Hinsey of the laboratory which was remarkably productive under Prof. C. R. Stockard.

For the first time, this year it was required that motion picture reels be sent to a committee in advance of the meeting. The chief reason was the fear lest a picture perfectly sound scientifically might cause serious embarrassment to local medical authorities through the activities of certain antagonistic groups. An informal committee comprised of nearly twenty of the members of the Cornell Medical College faculty

previewed the films submitted and advised that two of them should not be shown publicly. As a result of this recommendation these two films were presented by title. Of the six remaining reels submitted, one was placed on the Wednesday morning program, and the other five were presented between 7:15 and 9:00 on Wednesday evening, in the interval preceding the Smoker.

*Number of papers and demonstrations*

|                                   | 1942 | 1941 | 1940 |
|-----------------------------------|------|------|------|
| Papers from platform              | 134  | 138  | 132  |
| Papers withdrawn                  | 3    | 11   | 8    |
|                                   | —    | —    | —    |
| Papers actually presented         | 131  | 129  | 124  |
| Papers read by title              | 51   | 32   | 42   |
| Demonstrations (regular)          | 46   | 50   | 44   |
| Motion pictures as Demonstrations | 5    | 7    | 7    |
| Motion pictures with papers       | 2    | 2    |      |
| Motion pictures by title          | 2    | 2    | 1    |
|                                   | —    | —    | —    |
| Total motion pictures             | 9    | 11   | 8    |

For the Friday afternoon invitation program President Smith arranged a symposium on the general topic:

“Hormonal factors in sex inversion.” The four participants, with titles of their  $\frac{1}{2}$ -hour presentations, were:

C. H. Danforth: “Sex inversion in birds.”

R. R. Humphrey: “Sex inversion in Amphibia.”

R. R. Greene: “The effects of sex hormones on the embryonic sexual development of the rat.”

R. K. Burns, Jr.: “Hormones and experimental modification of sex in the opossum.”

SOCIAL ACTIVITIES

*Banquet.* President Smith, as toastmaster, introduced Dr. Joseph C. Hinsey who, as Acting Dean and as Professor of Anatomy at the Cornell University Medical College, welcomed the Association to New York. President Edmund E. Day gave a charming address of welcome on behalf of Cornell University. Anatomists were particularly delighted with his tribute to Simon H. Gage, one of the three charter members

of the Association, who at 91 is still active and productive. Alan Gregg, Director for Medical Sciences of the Rockefeller Foundation, gave a serious, prepared address in which he outlined his views on some aspects of the teaching of Anatomy. 169 persons attended.

*Smoker.* Approximately 350 members enjoyed the Smoker, as guests of the Cornell University Medical College.

*Tea.* A delightful tea was arranged by the wives of faculty members at the Medical School from 4:00 to 6:00 on Thursday, the afternoon of the demonstrations.

# MINUTES OF THE BUSINESS SESSIONS

WEDNESDAY, APRIL 1, 1942

*10:00 a.m.* At a brief Business Session President Smith announced the appointment of the following Committees:

*Auditing Committee:* Prof. C. V. Morrill, Chairman, Prof. P. B. Armstrong.

*Nominating Committee for 1943:* Prof. Harold Cummins, Chairman, Prof. Karl E. Mason, Prof. William F. Windle.

THURSDAY, APRIL 2, 1942

*12:15 p.m.* Principal Business Session, President Philip E. Smith in the chair. The President reported that the minutes of the Fifty-seventh Session were printed in The Anatomical Record, vol. 80, no. 1 (Supplement no. 1), May 26, 1941, pp. 1 to 3 and 7 to 22, and would not be read unless called for. On motion, duly made and seconded, the minutes were approved as printed.

*Report of the Treasurer:* The Secretary-Treasurer made the following report for the year 1941:

## *Financial statement for the year 1941*

|                                       |            |
|---------------------------------------|------------|
| Balance on hand in Checking Account,  |            |
| Dec. 31, 1940, last audit of accounts | 1,410.94   |
| Receipts from dues, etc.              | 1,302.34   |
|                                       | <hr/>      |
| <i>Total Credits</i>                  | \$2,713.28 |
|                                       | <hr/>      |

## Expenditures, 1941:

|                                                                                   |        |
|-----------------------------------------------------------------------------------|--------|
| Postage, stationery, supplies and miscel.                                         | 168.41 |
| Printing                                                                          | 48.82  |
| Programs, 57th Meeting                                                            | 91.33  |
| Secretarial assistance                                                            | 50.00  |
| Travelling expenses of Secretary                                                  |        |
| plus \$10 on hotel bill                                                           | 37.27  |
| Contribution to Union of Biological Societies                                     | 10.00  |
| Wistar Institute (691 abstracts at .50)                                           | 345.50 |
| Wistar Institute (720 Proceedings at .20,<br>plus reprints of Constitution, etc.) | 147.50 |
| Local Committee (57th Meeting)                                                    | 200.00 |
| Bank checks returned                                                              | 6.00   |

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*Total Expenditures* 1,104.83

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Balance on hand Dec. 31, 1941, and deposited in the name  
of the American Association of Anatomists in the First  
National Bank, Philadelphia, Pa.

1,608.45

Special Interest Account No. 10244, Morris Plan Bank,  
Philadelphia

|                                                 |        |
|-------------------------------------------------|--------|
| Balance, December 31, 1940                      | 686.19 |
| Interest ( $2\frac{1}{2}\%$ ) to April 30, 1941 | 8.58   |
| Interest ( $2\frac{1}{2}\%$ ) to Oct. 31, 1941  | 8.68   |

Balance December 31, 1941

703.45

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*Total Balance* \$2,311.90

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It will be noted that the checking account gained \$197.51 and the special account gained \$17.26 during the year, making a total gain of \$214.77.

*Report of the Auditing Committee:* Professor Morrill read the following report: "The undersigned Auditing Committee has examined the accounts of the Secretary-Treasurer for the year 1941, and finds total receipts reported to be those entered in the Journal, expenditures in accordance with receipted bills, and the balance on hand December 31, 1941, in agreement with the bank statement of that date and pass book of Special Account. The former shows a balance of \$1,608.45, and the latter a balance of \$703.45, making a total balance of \$2,311.90."

(Signed) CHARLES V. MORRILL  
PHILIP B. ARMSTRONG

On motion made and seconded the reports of the Treasurer and of the Auditing Committee were accepted and adopted.

*Election of Officers:* The Nominating Committee, consisting of Prof. C. G. Hartman, Prof. J. C. Hinsey and Prof. E. A. Boyden, Chairman, placed the following nominations before the Association:

For President, to serve for 2 years, Prof. Edgar Allen; for First Vice-President, Prof. J. Parsons Schaeffer; for Second Vice-President, Prof. L. B. Arey, both for 2-year terms; for Secretary-Treasurer, Prof. Francis H. Swett for a term of 4 years; for Members of the Executive Committee, for the term expiring in 1946, Prof. S. I. Kornhauser and Prof. Sam L. Clark—all terms mentioned being those specified in the Constitution.

In the absence of additional nominations, a motion was made, seconded and carried that the Secretary cast a unanimous ballot for the above-named nominees, and they were declared elected.

*Election of Representatives:* The Secretary read, in behalf of the Executive Committee, the following nominations: Representative on the Commission for Standardization of Biological Stains for 1 year (in place of Dr. Harold Davenport on leave because of war service): Prof. William F. Windle; Representatives to the Council of the American Association for the Advancement of Science for 1 year: Profs. J. C. Hinsey and Philip E. Smith—the terms of service being those specified in the Orders of the Association.

In the absence of other nominations, the above nominees were duly elected.

*New Members:* The Secretary presented the following forty-two names of persons recommended by the Executive Committee for election to membership in the Association, the names in parentheses indicating the sponsors:

ADES, HARLOW WHITING, B.S., M.S., Ph.D., Instructor in Anatomy, *Emory University, Emory, Ga.* (F. B. Adamstone, H. Blincoe.)

D'ANGELO, SAVINO A., B.S., M.S., Ph.D., Assistant Instructor in Biology, *New York University, New York City.* (H. A. Charipper, R. Gaunt.)

- BARRY, ALEXANDER, A.B., M.A., Ph.D., Instructor in Anatomy, *University of Michigan, Ann Arbor, Mich.* (B. M. Patten, R. E. McCotter.)
- BENTON, JOSEPH G., A. B., M.S., Ph.D., Assistant in Physiology, *New York University College of Medicine, New York City.* (M. M. Hoskins, W. J. Krieg.)
- BOGART, RALPH, B.S., M.S., Ph.D., Agent in Animal Husbandry, Bureau of Animal Husbandry, U. S. Department of Agriculture; Instructor in Animal Husbandry, *University of Missouri, Columbia, Mo.* (F. F. McKenzie, M. D. Overholser.)
- BOLING, JOHN LANDRUM, A.B., Ph.D., Research Assistant in Neuro-Anatomy, *Yale University, New Haven, Conn.* (H. S. Burr, R. G. Meader.)
- BRODIE, ALLAN G., D.D.S., Ph.D., Professor of Orthodontia and Head of the Department, *College of Dentistry, University of Illinois, Urbana, Ill.* (O. F. Kampmeier, G. von Bonin.)
- BURACK, ETHEL, A.B., Ph.D., Instructor in Anatomy, Research Associate in Pathology, *Albany Medical College, Albany, N. Y.* (J. M. Wolfe, J. L. Schwind.)
- CASTELNUOVO, GINA, Ph.D., Research Assistant in Zoology, *University of Missouri, Columbia, Mo.* (M. J. Guthrie, E. Witschi.)
- CHASE, PHILENA EVANS, B.A., Ph.D., Instructor in Histology and Embryology, *Temple University, Philadelphia, Pa.* (S. R. Detwiler, J. F. Huber.)
- CRAFTS, ROGER CONANT, B.S., Ph.D., Instructor in Anatomy, *Boston University, Boston, Mass.* (J. L. Conel, L. C. Fogg.)
- DEY, FREDERICK L., A.B., M.S., Ph.D., Research Fellow in Neurology, *Northwestern University, Chicago, Ill.* (S. W. Ranson, H. W. Magoun.)
- ELLIOTT, HARRY CHANDLER, A.B., M.A., Ph.D., Banting Research Fellow in Anatomy, *University of Toronto, Toronto, Canada.* (J. C. B. Grant, A. W. Ham.)
- EVERSOLE, WILBURN J., A.B., M.S., Ph.D., Assistant Instructor in Biology, *New York University, New York City.* (R. Gaunt, R. Rugh.)
- FRIEDMAN, SYDNEY MURRAY, B.A., M.D., M.S., Teaching Fellow in Anatomy, *McGill University, Montreal, Canada.* (C. P. Martin, H. Selye.)
- GARDNER, ERNEST DEAN, B.S., M.D., Instructor in Anatomy, *Stanford University*, on leave 1941-1942 at *Washington University, St. Louis, Mo.* (J. E. Markee, C. H. Danforth.)
- GARRETT, FREDERIC DAUGHERTY, A.B., Ph.D., Instructor in Anatomy, *University of Nebraska, Omaha, Neb.* (J. S. Latta, C. W. M. Poynter.)
- GILLILAN, LOIS A., B.A., A.M., Ph.D., Dr. Louis Merwin Gelston Fellow, *University of Michigan, Ann Arbor, Mich.* (C. J. Herrick, E. C. Crosby.)
- GRAY, DONALD JAMES, B.S., M.S., Ph.D., Assistant Professor of Anatomy, *Stanford University, Stanford, Calif.* (C. H. Danforth, J. E. Markee.)
- GROAT, RICHARD A., Ph.D., Instructor in Anatomy, *Emory University, Emory, Ga.* (H. W. Mossman, F. D. Geist.)
- GRUENWALD, PETER, M.D., Associate in Embryology, *The Chicago Medical School, Chicago, Ill.* (J. J. Sheinin, L. B. Arey.)
- HARMAN, PINCKNEY J., B.S., M.S., Ph.D., Instructor in Anatomy, *Georgetown University School of Medicine, Washington, D. C.* (G. H. Daron, O. Solnitzky.)

- HASHIMOTO, EDWARD I., A.B., M.D., M.S., Associate Professor of Anatomy, *University of Utah Medical School, Salt Lake City, Utah.* (C. B. Freudenberg, C. A. Swinyard.)
- KAMMERAD, ADRIAN, A.B., Ph.D., Instructor in Anatomy, *Louisiana State University School of Medicine, New Orleans, La.* (B. I. Burns, D. D. Baker.)
- MACLEOD, JOHN, A.B., M.S., Ph.D., Research Associate in Anatomy, *Cornell University Medical College, New York City.* (J. C. Hinsey, C. V. Morrill.)
- MORISON, ROBERT SWAIN, A.B., M.D., Assistant Professor of Anatomy, *Harvard Medical School, Boston, Mass.* (G. B. Wislocki, A. L. Grafflin.)
- NIELSON, PAUL E., M.S., Ph.D., Research Fellow in Anatomy, *Washington University, St. Louis, Mo.* (H. W. Mossman, F. D. Geist.)
- REED, ADRIAN FARAGHER, A.B., M.A., Ph.D., Assistant Professor of Gross Anatomy, *Tulane University of Louisiana, New Orleans, La.* (W. C. Smith, H. Cummins.)
- RISLEY, PAUL LEMUEL, B.A., M.S., Ph.D., Assistant Professor of Zoology, *State University of Iowa, Iowa City, Ia.* (E. Witschi, R. K. Burns, Jr.)
- SALMON, THEODORA NUSSMAN, B.A., M.A., Ph.D., Instructor in Biology, *Hunter College, New York City.* (B. L. Maclean, H. H. Shapiro.)
- SAUER, MARY ELMORE, B.A., M.A., Ph.D., Instructor in Histology and Embryology, *University of Texas Medical School, Galveston, Tex.* (D. Duncan, H. C. Tracy.)
- SCHAEFFER, BOBB, A.B., A.M., Ph.D., Associate in Histology and Embryology, *Jefferson Medical College, Philadelphia, Pa.* (A. J. Ramsay, G. A. Bennett.)
- SCHOTTÉ, OSCAR E., Lic. Sc. Phys. et Nat., Doct. Sc. Nat., Geneva, Switzerland, Associate Professor of Biology, *Amherst College, Amherst, Mass.* (E. G. Butler, H. S. Emerson.)
- SIMPSON, WILLIAM LOYAL, B.S., Ph.D., Research Associate in Cytology, Washington University and Barnard Free Skin and Cancer Hospital, *Washington University, St. Louis, Mo.* (G. H. Scott, E. V. Cowdry.)
- SINCLAIR, JOHN G., B.S., M.S., Ph.D., Professor of Histology-Embryology, *University of Texas, Medical Branch, Galveston, Tex.* (D. Duncan, H. W. Mossman.)
- SPRAGUE, JAMES MATHER, A.B., A.M., Ph.D., Teaching Fellow in Biology, *Harvard University, Museum of Comparative Zoology, Cambridge, Mass.* (A. B. Howell, W. L. Straus, Jr.)
- STOWELL, ROBERT E., A.B., M.D., Research Fellow, Washington University and Barnard Free Skin and Cancer Hospital, *Washington University, St. Louis, Mo.* (E. V. Cowdry, R. C. MacCardle.)
- VAN DYKE, JOHN HOWARD, A.B., M.S., Ph.D., Research Histologist, *U. S. Nutrition Laboratory, Ithaca, N. Y.* (H. B. Adelman, J. W. Papez.)
- WEAVER, HARRY MERWYN, A.B., M.S., Ph.D., Instructor in Anatomy, *Wayne University College of Medicine, Detroit, Mich.* (W. O. Nelson, E. Cutuly.)
- WEINSTEIN, BENJAMIN BERNARD, B.S., M.D., M.S., Instructor in Gross Anatomy and Gynecology, *Tulane University of Louisiana, New Orleans, La.* (W. C. Smith, H. Cummins.)
- WILLIAMS, WILLIAM LANE, B.S., M.A., Ph.D., Instructor in Anatomy, *The University of Rochester, School of Medicine and Dentistry, Rochester, N. Y.* (K. E. Mason, Edgar Allen.)
- YEAKEL, ELEANOR H., A.B., M.A., Ph.D., Fellow, *The Wistar Institute of Anatomy and Biology, Philadelphia, Pa.* (E. J. Farris, H. D. King.)

Before the ballot on new members, the Secretary reported that the Executive Committee had voted to recommend to the Association the following modification of the usual requirements for membership (the new portions being printed in italics):

“The Executive Committee usually recommends for membership only those candidates who have received the doctor’s degree (*M.D. or Ph.D.*) or have had equivalent experience and training, and who have *either published at least one independent, definitive paper — or who have, on reliable testimony, been chiefly responsible for one or more of several substantial papers of joint authorship* — upon (an) anatomical or cognate subjects.”

It was moved, seconded and passed that this recommendation be adopted.

On motion, duly seconded, the Secretary was then instructed to cast a ballot for all candidates proposed by the Executive Committee, and they were declared elected.

*Members placed in the category of “members relieved of the payment of dues”*: The Secretary reported that, by vote of the Executive Committee, eleven members had been placed in this category in accordance with the provision of Article VI, Section II of the Constitution, which reads: “Any member who has paid the annual dues for thirty years, or who has attained the age of sixty-five years, or who has retired because of illness, may be relieved of the payment of the annual dues at the discretion of the Executive Committee.” It was stated that nineteen had been placed in this category previously, of whom three have died, making a present total of twenty-seven.

*Members in countries in Europe and Asia which are at war*: The Secretary has received a number of very appreciative letters from members in the British Isles, in response to the notification of the action of the Association, at the 1941 session, excusing them from payment of dues for the duration of the war.

*Members deceased*: The Secretary presented the following statement of the Executive Committee:

The Association has suffered very great loss through the death during the year of six members:

GEORGE ELLETT COGHILL, born March 17, 1872, died July 23, 1941. Elected to membership in 1904. Private investigator, Gainesville, Florida. Formerly Professor of Anatomy, University of Kansas; Professor of Comparative Anatomy, The Wistar Institute. A member of the Executive Committee 1927 to 1931; President, 1932 to 1934. (A resolution on the death of Doctor Coghill has been adopted at this meeting and is printed on pages 131 to 137 of these Proceedings.)

ALLEN KRAMER KRAUSE, born February 13, 1881, died May 12, 1941. Elected to membership in 1919. Lecturer in Medicine at Johns Hopkins. Previously associated with the Saranac Laboratories, the Desert Sanatorium, Stanford and the University of California. A world authority on tuberculosis. Brilliant investigator, lecturer and editor.

DEAN DEWITT LEWIS, born August 11, 1874, died October 9, 1941. Identified with the University of Chicago for nearly 30 years, later with the Johns Hopkins University, where he was Emeritus Professor of Surgery at the time of his death. Carried into Surgery, in which he was a leader, a lively interest in Anatomy, acquired during 3 years as Instructor of Anatomy, and which yielded anatomical contributions that definitely enriched the field.

PAUL STILWELL MCKIBBEN, born March 14, 1886, died November 11, 1941. Elected to membership in 1912. Professor of Anatomy and Dean, University of Southern California. Had previously occupied positions in Anatomy at the University of Chicago, the University of Western Ontario and the University of Michigan, and had engaged in neurological research at Johns Hopkins during the first World War. Fields covered by investigations included: the nervus terminalis; eye-muscle nerves and peripheral olfactory apparatus of Amphibia; cerebrospinal fluid pressure and brain bulk; and lymphatics.

JUAN CANCIO NAÑAGAS, born October 20, 1891, died June, 1941. Elected to membership in 1921. Professor of Anatomy, College of Medicine, University of the Philippines, Manila. Graduate, University of the Philippines. Supplementary training Johns Hopkins, University of Chicago, University of Minnesota, University College, London, and Madrid (Ramón y Cajal). Published over seventeen valuable contributions to Anatomy, principally anthropological studies of Filipinos. Staunch builder of that sturdy people which is at this moment sharing fame and glory of General MacArthur.

AUGUST HERMSMELER WITTENBORG, born September 4, 1883, died August 21, 1941. Elected to membership in 1916. Professor of Anatomy, University of Tennessee. An inspiring and greatly beloved teacher of Gross Anatomy at the University of Tennessee for 39 years.

*Member resigned:*

J. J. Keegan, Omaha, Neb.

*Members dropped for non-payment of dues for 1940 and 1941:*

Adrian Buyse, Rochester, N. Y.

R. L. Carpenter, Boston, Mass.

J. B. Goldsmith, Oklahoma City, Okla.

C. W. Harwell, Emory, Ga.

M. H. Spaulding, Bozeman, Mont.

(The Constitution, in Article VI, Section I, provides that former members "may be reinstated at the discretion of the Executive Committee on payment of arrears".)

*Number of members:* The Secretary presented the following statistics on membership:

|                                   |     |
|-----------------------------------|-----|
| Number of members April 11, 1941  | 720 |
| Deceased                          | 6   |
| Resigned                          | 2   |
| Dropped                           | 5   |
|                                   | 13  |
|                                   | —   |
|                                   | 707 |
| New members elected April 2, 1942 | 42  |
|                                   | —   |
| Number of members April 3, 1942   | 749 |

The various items on membership presented by the Secretary were then adopted by the Meeting.

*Payment to Local Committee:* In view of the mounting costs to the Local Committee, due in part to the steady increase in membership, it was reported that the Executive Committee recommended that the amount to be allotted be increased from \$200 to \$250. On motion duly made and seconded it was voted that the Treasurer be authorized to pay the sum of \$250 from the general funds of the Association to the Local Committee on arrangements, to aid in defraying the cost of entertainment of the Association during the present meeting. The Secretary-Treasurer suggested that the possibility be considered of a further increase to \$300 in subsequent years, explaining that the treasury could take care of such an increase.

*Dues for 1942:* The Secretary-Treasurer reported that the Executive Committee recommends that the dues for 1942 be continued at \$2.00. It was explained that this amount finances, in addition to regular expenses, the automatic sending of "Abstracts" and "Proceedings" to each member; notices, "Abstracts" and "Proceedings" sent to non-paying members, and to members in foreign countries involved in the war; the increased amount appropriated to the Local Committee; with a comfortable annual surplus available for emergencies.

A motion was made, seconded and passed that the dues for 1942 be \$2.00.

*Place of next meeting:* The Secretary reported the following action: The Executive Committee has voted to accept the invitation of Principal and Vice-Chancellor Cyril James and Prof. C. P. Martin of McGill University, to hold the 1943 meeting in Montreal, Canada, on Wednesday, Thursday and Friday, April 21, 22, 23, in the week preceding Easter, which falls on April 25 in 1943.

It was further reported that, for the 1944 meeting, the University of Wisconsin at Madison was favored by the Committee.

Gratitude was expressed to Washington University, St. Louis, for an invitation to meet there in 1944, and to the several other "western" schools from which the Association has continuing invitations.

Regarding the Montreal meeting next year, the Secretary reported that he had communicated with our State Department, inquiring regarding possible border difficulties, and had received a reassuring reply from G. Howard Shaw, Assistant Secretary of State, in which he saw no objection to our acceptance of the invitation, explaining that each individual should merely "carry with him some evidence of his American citizenship, such as a cancelled passport, birth certificate, naturalization certificate, lodge cards, automobile driving license, etc. to exhibit to the American immigration authorities upon return to the United States". Members in the United States who are not citizens "may apply to the Immigration and Naturalization Service, Department of Justice, Fifteenth and Chestnut Streets, Philadelphia, Pa. for permits to reenter this country. Aliens who present such permits issued with the concurrence of the Secretary of State as to destination are exempt from obtaining permits to depart from the United States". In addition, it will be necessary for aliens to obtain permission from the Canadian Immigration Authorities at Ottawa.

Regarding demonstration material, including motion picture films, some information has already been obtained and further details will be arranged by the Secretary, which will be explained in the Notice of the 1943 meeting.

It is obvious that there are no serious difficulties involved and the hope was expressed that no member would be deterred from planning to attend because the meeting place was to be across the border.

*The journals:* The Secretary reported for the Executive Committee that the selection by the Committee at the 1941 meeting, of Philip E. Smith as Managing Editor of The American Journal of Anatomy, to take the place left vacant by George W. Corner's resignation, was endorsed by The Wistar Institute, owner of the journal, and that Doctor Smith assumed his new duties on May 26, 1941 — his name first appearing on the cover of volume 69, number 1, July 1941. Doctor Smith reported the enlargement of the Board of Associate Editors from 4 to 5 by the appointment of J. C. Hinsey and B. M. Patten, one of them to replace W. J. Atwell, deceased.

Regarding journals: For the benefit of new members it was again pointed out that The American Journal of Anatomy and The Anatomical Record, while owned by The Wistar Institute of Anatomy and Biology, are sponsored by the American Association of Anatomists, which selects their Managing Editors, subject to the approval of The Wistar Institute; and that members of the Association are granted a reduction of 25% from the regular subscription rates, not

only of these two journals, but also of all Wistar journals, including *The Journal of Comparative Neurology* and the *Journal of Morphology*.

*Report of H. A. Davenport on Commission for Standardization of Biological Stains:* The Secretary stated that he had received and filed a report dated May 6, 1941, on the activities of the Commission.

*Letter from Dr. John Beattie:* The Secretary reported the receipt of the following letter which was read to the meeting:

ROYAL COLLEGE OF SURGEONS OF ENGLAND  
BERNHARD BARON RESEARCH LABORATORIES  
Prospect House, Finchingfield, Braintree, Essex

5th March, 1942.

Dear Dr. Clark,

This is just a little note of greeting and good wishes for the success of the Meeting in New York in April. It is good to know that in spite of the distractions of the war the work of the Association is going forward, and I hope that it will not be long before I shall be able to join you at the first Meeting after peace has come again.

With kindest regards, and all good wishes to yourself and the Members of the Association,

Yours sincerely,

(Signed) John Beattie.

*Report of the Committee on National Defense:* The report of J. S. Nicholas, Chairman, reached the Secretary in the form of a letter as follows:

Dear Dr. Clark:

February 27, 1942

I received your letter yesterday asking for information concerning the outlook for the anatomists in the role of national assistance. I have been in constant touch with this through the offices of the National Roster and would like to report that the anatomists have, with a few minor exceptions, responded nobly to the request for information on their entire background and have in the main returned their questionnaires to the Roster. They have all been classified according to their main interests and will be called if it should become necessary. The Services, however, realize that the men who constitute the body of the anatomists are in general much more valuable as trainers of men for future medical posts than in any other capacity in which they might be considered. If the war is of short duration, it is totally unnecessary to call anatomists from their posts for work in which they would not be as efficient as they are in their home territory. If the war is to be a long one, it will become increasingly necessary for the anatomists

to do more work in the posts which they now hold. General Hershey's office has been very succinct in carrying this attitude with reference to anatomists. They, however, have not always been able to hold strictly to it because of their relationships with the local draft board.

One factor should be made public to the members of the Anatomists Association and that is that if at any time any members are subject to draft or called to duty as Reserve Officers at the expense of vital work or training at their local posts, they should immediately forward any desires for transfer or new assignment or deferment to the National Roster of Specialized and Scientific Personnel, Washington, D. C. This should be documented in full and if the individual has not completed the filling out of the questionnaire he should write to this bureau for a definite questionnaire so that his case can be reviewed. I feel that this is essential if we are to preserve our anatomists in those positions and places where they are doing the most good.

If any anatomist feels that he is not essential in his present post and has the urge to do something which is more active and more directly connected to the national effort, it would be of especial interest for us to know of it, especially of any anatomist who has done advanced work along physical lines and particularly one who might be adept in designing, maintaining, or repairing radio apparatus. This is an essential in which the National Roster has found our country to be most deficient in raw supplies. If there are any anatomists who would qualify under this, it would be exceedingly helpful if they would write to Dr. Bailey at the National Research Council, 2101 Constitution Avenue, Washington, D. C.

I hope you will bring this to the attention of the Executive Committee and I shall offer it as the report of our Committee unless I hear objections from you and Philip Smith.

Sincerely yours,

(Signed) J. S. Nicholas.

The report, endorsed by the other two members of the Committee, was adopted by the Meeting. Doctor Nicholas gave a lively and instructive talk, in which he stressed the vital importance of anatomists in the training of medical students and urged that they continue in their present positions and strive to maintain high standards.

It was reported that the Executive Committee had voted to continue the Committee on National Defense.

*The Committee on Anatomical Nomenclature:* The Secretary reported that the Executive Committee had appointed George W. Corner Chairman of this Committee, with authorization to select additional members. Doctor Corner explained briefly the status of the Committee's activities, indicating a determination to salvage the results of the Committee's extensive past studies of nomenclature revision.

*Report of the Motion Picture Advisory Committee:* The following report was presented and accepted by the Meeting:

The Committee appointed to cooperate with The Wistar Institute, in its project involving the formation of a depository and central clearing-house for films of biological interest, has continued through a second year to view and to write reviews of films of especial interest to anatomists. These reviews, along with others, have been printed in various numbers of *The Anatomical Record* during the past year; and in *The Anatomical Record*, vol. 82, pp. 261, 262, 1942, a complete list has been published of the 26 films which have been approved to date. It is reported by Doctor Farris of The Wistar Institute, that the project has aroused wide-spread interest, scarcely a day passing without one or more inquiries regarding them.

The Committee recommends:

(a) That the Executive Committee appoint *annually* a committee to cooperate with The Wistar Institute in this project.

(b) That the Association encourage its members to submit films to The Wistar Institute for evaluation, and to contribute a copy of each approved film to the depository in order to have at one location a complete collection of films of anatomical interest.

W. H. LEWIS

C. C. SPEIDEL

ELIOT R. CLARK, Chairman.

*Delegates to Celebration:* For information it was reported that the American Association of Anatomists was represented at two anniversary celebrations by delegates appointed by President Smith as follows: At the Fiftieth Anniversary Celebration of The University of Chicago September 27-29, 1941, by Prof. S. W. Ranson; and at the One hundred seventy-fifth Anniversary of the Founding of Rutgers University, October 9-10, 1941, by Prof. C. F. W. McClure. Notes of appreciation have been received from Presidents of both universities.

*The National Science Fund:* The Secretary read the following statement:

At the request of Dr. William J. Robbins, Chairman of the Board of Directors, and of President I. Langmuir of the A.A.A.S., attention is called to the creation in the spring of 1941, by the National Academy of Sciences, of a "National Science Fund", to serve as a means of helping to meet an increasingly urgent need for additional funds to support fundamental scientific research. Anatomists can help in the building up of the Fund, by suggesting to persons of means that they denote to, or include in their wills donations to, this Fund. The Chairman of the Board will gladly supply specific information to all who are interested; his address is: Dr. William J. Robbins, 515 Madison Ave., New York City.

*Publication of 1942 Symposium Papers:* President Smith announced that the papers to be given at the Friday afternoon symposium would be published by the Cattell Press, in the "Biological Symposia" series, along with several papers in the same field that were presented at The University of Chicago as a part of the Fiftieth Anniversary Celebration. Thanks were expressed to The Wistar Institute of Anatomy and Biology, which, in response to an inquiry of the Secretary, had signified a willingness to print them as a small monograph if the Association wished.

*Resolution of Appreciation:* The following resolution, proposed by Prof. G. W. Corner, was adopted unanimously:

The members of the American Association of Anatomists pause in the midst of their Fifty-eighth Session, to record their gratitude to the Cornell University Medical College and the hospitality and efficiency of the Local Committee, which is making the meeting happy and successful in every way. We congratulate the Medical College upon the accomplishments of the Department of Anatomy under Dr. Hinsey and his colleagues. To the Management of the Hotel Commodore we add our thanks for the excellent arrangements made for the meeting.

*Resolution of Appreciation to the University of Pennsylvania:*

On motion by Edgar Allen the following resolution, prepared by President P. E. Smith, was adopted:

The American Association of Anatomists expresses its deep appreciation to the University of Pennsylvania for the aid and facilities which it has generously extended to the Association through Professor Eliot R. Clark, during his four-year term as Secretary-Treasurer.

*Resolution regarding Secretary-Treasurer:* The following resolution, proposed by W. H. Lewis, was adopted:

Resolved: that the American Association of Anatomists express to Eliot R. Clark its very great appreciation of his services during his four-year term as Secretary-Treasurer.

*Omission of Concluding Business Session:* President Smith announced that, unless special business required, the concluding business session scheduled for Friday at 12:45 P.M. would be omitted.

The Business Session adjourned at 1:10 P.M.

ELIOT R. CLARK

Secretary of the Fifty-eighth Session of  
the American Association of Anatomists.

*Postscript by the Secretary:* As the Secretary-Treasurer comes to the end of his 4-year term, he wishes to express his very great appreciation of the rare privilege which was granted him by the members of the Association when they elected him to this office. While the duties involved have been considerable, the time expended has been compensated for many fold by the opportunity which has been afforded for intimate contact with fellow-members. In carrying out his tasks, the Secretary-Treasurer has been aided enormously by the generous cooperation of the entire membership, and particularly by the competence of the various Local Committees headed, at Boston by Doctor Wislocki, at Louisville by Doctor Kornhauser, at Chicago by Doctor Swift, and at the present meeting by Doctor Hinsey; and by the very friendly and helpful cooperation of Doctor Farris and Miss Lawton of The Wistar Institute. His work has been greatly facilitated by the marked executive ability of two great Presidents of the Association, Prof. S. W. Ranson and Prof. P. E. Smith; and the pleasure of the task has been enhanced by the privilege of working with them.

Both the Association and the Secretary-Treasurer owe a large debt of gratitude to Miss Anna M. Shields, Department Secretary of the Anatomy Department of the University of Pennsylvania, who has cheerfully added to her already heavy duties the day-in, day-out keeping of Treasurer's records, the unending renovation of address lists, and the large mass of special typing and correspondence which both precede and follow the annual meeting. The Association is further indebted to the University of Pennsylvania for generous loan of personnel, space and facilities.

It has been the endeavor of the Secretary-Treasurer to do all within his power to retain those fine traditions which have made our Association not only effective scientifically, but a source of delight to its members. He is sure that many will share his conviction that, insofar as this has been accomplished, a very considerable portion of the success has been due to the other member of the pair, once designated by Doctor Bardeen as "the double-E. Clarks." E. R. C.

## AMERICAN ASSOCIATION OF ANATOMISTS

### Officers

|                                    |                          |
|------------------------------------|--------------------------|
| <i>President</i> .....             | Edgar Allen              |
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| <i>Second Vice-President</i> ..... | Leslie B. Arey           |
| <i>Secretary-Treasurer</i> .....   | Francis Huntington Swett |

### Executive Committee

|                             |                                      |
|-----------------------------|--------------------------------------|
| For term expiring 1943..... | Stacy R. Guild, Edward A. Boyden     |
| For term expiring 1944..... | Joseph C. Hinsey, Carl C. Speidel    |
| For term expiring 1945..... | E. Horne Craigie, Walter E. Sullivan |
| For term expiring 1946..... | Sam L. Clark, S. I. Kornhauser       |

*Delegates to the Council of A.A.A.S. for 1942*

Joseph C. Hinsey  
Philip E. Smith

*Representative to the National Research Council 1940-1943*

Eliot R. Clark

*Member of the Commission on Standardization of Biological Stains*

William F. Windle

*Delegate of Union of Biological Societies, 1941-1944*

Stacy R. Guild

## Committee on Nominations for 1942

Harold Cummins, *Chairman*

Karl E. Mason

William F. Windle

## Committee on Anatomical Nomenclature

George W. Corner, *Chairman*

## Committee on National Defense

J. S. Nicholas, *Chairman*

The President and Secretary-Treasurer, ex officio

*Motion Picture Committee*

E. R. Clark, *Chairman*

Warren H. Lewis

Carl C. Speidel

## MEMBERS

- ABELL, RICHARD G., A.M., Ph.D., Associate in Anatomy, *University of Pennsylvania School of Medicine, Philadelphia, Pa.*
- ABERCROMBIE, WARREN F., A.B., Sc.M., Ph.D., Head of Biology Department, *Erskine College, Due West, S. C.*
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- ALLEN, WILLIAM F., A.M., Ph.D., Head of Department of Anatomy, *University of Oregon Medical School, Portland, Ore.*
- ALLIS, EDWARD PHELPS, JR., C.E., M.D., LL.D. (Charter member), *Palais de Carnoles, Menton (A.M.), France.*
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- APGAR, CHARLES S., JR., Ph.D., R.D. No. 3, Harrisburg, Pa.
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- ASDELL, SYDNEY ARTHUR, M.A., Ph.D., Professor of Animal Physiology, State College of Agriculture, Cornell University, Ithaca, N. Y.
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- BAILEY, PERCIVAL, M.D., Ph.D., Professor of Neurology and Neurosurgery, University of Illinois, 1853 W. Polk St., Chicago, Ill.
- BAILEY, RALPH JORDAN, B.S., M.S., Ph.D., Assistant Professor of Anatomy, School of Medicine, University of Arkansas, Little Rock, Ark.
- BAILLIF, R. N., Ph.D., Instructor in Anatomy, Louisiana State University, Medical Center, New Orleans, La.
- BAITSELL, GEORGE ALFRED, B.S., M.A., Ph.D., Professor of Biology, Yale University, Osborn Zoological Laboratory, New Haven, Conn.
- BAKER, DAN D., M.A., M.D., Associate Professor of Anatomy, Louisiana State University, Medical Center, New Orleans, La.
- BAKER, R. C., A. B., M.A., Ph.D., Professor of Anatomy, Department of Anatomy, Hamilton Hall, Ohio State University, Columbus, O.
- BAKER, ROGER D., M.D., Assistant Professor of Pathology, Duke University, Durham, N. C.
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- BARRETT, W. C., JR., Ph.D., Assistant Professor of Histology and Embryology, School of Medicine, Western Reserve University, Cleveland, O.
- BARRIS, RALPH W., Ph.D., Assistant Professor of Anatomy, George Washington University Medical School, Washington, D. C.

- BARRON, DONALD H., B.A., M.S., Ph.D., *Department of Zoology, University of Missouri, Columbia, Mo.*
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- BARTELMEZ, GEORGE W., Ph.D. (Vice-Pres. '32-'34, Exec. Com. '36-'40). Professor of Anatomy, *The University of Chicago, Chicago, Ill.*
- BARTSCH, PAUL, B.S., M.S., Ph.D., D.Sc., Curator of Mollusks and Cenozoic Invertebrates, *U. S. National Museum, Washington, D. C.*
- BAST, T. H., B.A., Ph.D., Professor of Anatomy, *University of Wisconsin, 308 Science Hall, Madison, Wis.*
- BATSON, O. V., A.M., M.D., Professor of Anatomy, *Department of Anatomy, Graduate School of Medicine, University of Pennsylvania, Philadelphia, Pa.*
- BAUMGARTNER, WILLIAM J., A.B., A.M., Ph.D., Professor of Zoology, University of Kansas, 1209 Ohio St., Lawrence, Kan.
- BEAMS, HAROLD W., Ph.D., Professor of Zoology, *State University of Iowa, Iowa City, Ia.*
- BEAN, ROBERT BENNETT, B.S., V.P.I., M.D., Professor of Anatomy, University of Virginia, Box 1536, University Station, Charlottesville, Va.
- BEATON, LINDSAY E., A.B., M.S., M.D., Medical Fellow, National Research Council, *Northwestern University Medical School, Chicago, Ill.*
- BEATTIE, JOHN, M.D., D.Sc., Conservator of Museum and Director of Research, Royal College of Surgeons; Colonel, Army Medical Service; *Royal College of Surgeons, Lincoln's Inn Fields, London, W.C.2, England.*
- BECKER, R. FREDERICK, B.S., M.S., Ph.D., Instructor in Microscopic Anatomy, *Northwestern University Medical School, Chicago, Ill.*
- BÉLANGER, LEONARD F., A.B., M.D., A.M., Assistant Professor of Histology (on leave); on active service with the R. C. A. F., *University of Montreal, Montreal, Canada.*
- BENJAMIN, JAMES W., A.B., M.S., Ph.D., Associate Professor of Histology, Embryology and Neuroanatomy, *New York Medical College, Flower and Fifth Avenue Hospitals, New York City.*
- BENNETT, GEORGE A., A.B., M.D., Assistant Professor of Anatomy, *Daniel Baugh Institute of Anatomy, Jefferson Medical College, Philadelphia, Pa.*
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